

BONE AND THE HEMATOPOIETIC AND IMMUNE SYSTEMS

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P.T.

National Institute of Arthritis and Musculoskeletal and Skin Diseases

National Institute on Aging

National Institute of Dental and Craniofacial Research

National Institute of Diabetes and Digestive and Kidney Diseases

National Heart, Lung, and Blood Institute

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 ANNOUNCEMENT.

PURPOSE

The participating Institutes seek investigator-initiated projects that have the potential to illuminate functional interactions between bone and the hematopoietic and immune systems. Recent observations underscore the linkage between endochondral bone formation and the establishment of hematopoietic marrow, and suggest that interactions between bone, marrow, and the immune system persist in the mature skeleton. Marrow stromal cells include the precursors of the osteochondrogenic lineage, exert important influences on osteoclastogenesis and lymphopoiesis, and mediate the effects of some systemic factors on bone turnover. Recent evidence indicates that hematopoietic cells can influence the differentiation of osteogenic cells, and suggests that mature lymphocytes can influence osteoclastic and osteoblastic functions. In order to explore the mechanisms that underlie these interactions, the participating Institutes will support outstanding projects that have the potential to either clarify the importance of specific cell types and effector molecules or identify previously unrecognized cellular and molecular agents that influence bone physiology. Collaborations among bone biologists, hematologists, and immunologists, and between basic scientists and clinical investigators, will be particularly encouraged.

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, Bone and the Hematopoietic and Immune Systems, is related to the priority area of Diabetes and Chronic Disabling Conditions by virtue of its relevance to osteoporosis and other conditions of bone loss and increased fracture risk. Potential applicants may obtain a copy of "Healthy People 2000" at <http://www.crisny.org/health/us/health7.html>

ELIGIBILITY REQUIREMENTS

Applications for research project (R01) support may be submitted by domestic and foreign, for-profit and non-profit organizations, public and private, such as universities, colleges, hospitals, laboratories, units of State and local governments, and eligible agencies of the Federal government. Foreign institutions are not eligible for program project (P01) grant support. 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 and program project grant (P01) mechanisms. Program project grants may be effective mechanisms for facilitating interdisciplinary collaborations. However, policies on the acceptance and funding of program project applications vary among the participating institutes. Therefore, investigators are strongly urged to contact appropriate institute staff before preparing P01 applications. Investigators may also wish to consider the Interactive Research Project Grant mechanism (<http://www.nih.gov/grants/guide/pa-files/PA-96-001.html>) as a means of coordinating related projects. Responsibility for the planning, direction, and execution of the proposed project will be solely that of the applicant. The total project period for an application submitted in response to this PA may not exceed 5 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, which applies to R01 grant applications with total direct costs not exceeding \$250,000 per year, 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>. Highlights of the new format are noted below.

- o Modular grant 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.

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

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

- o 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.

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

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

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

- o Additional budget information will be requested only under special circumstances.

RESEARCH OBJECTIVES

Background

The interdependence of bone and the hematopoietic system has long been apparent. In the higher vertebrates, development of bone marrow occurs in conjunction with the process of endochondral bone formation. During this process, establishment of the marrow environment depends upon the excavation of hypertrophic cartilage and bony trabeculae by osteoclasts, which arise from the hematopoietic monocyte-macrophage lineage. Marrow stromal cells include the progenitors of the osteoblastic lineage and are the sources of effector molecules that support and regulate both hematopoiesis and bone remodeling. During remodeling of cancellous bone, both osteoclasts and osteoblasts function in close apposition to hematopoietic cells. Yet much remains to be learned about the cellular and molecular signaling pathways that operate between the many different cell types present in the marrow.

Relationships between bone and the immune system are less obvious. Osteopetrotic syndromes, arising from deficiency of bone resorption, often include associated immune defects. However, this seems most often to be a secondary consequence of the failure to establish a normal hematopoietic environment. Glucocorticoids and other immunosuppressant drugs are observed in the clinic to precipitate a net loss of bone that can predispose to fracture. Similarly, many cytokines and other regulatory molecules that are important regulators of immune cell differentiation and maturation also have potent effects on osteoblasts and osteoclasts. However, it is for the most part unclear whether these parallels reflect interaction between bone cells and immune cells, or instead, independent effects of the agents.

The scientific workshop "Bone and the Hematopoietic and Immune Systems" was convened in August, 1997 by the National Institutes of Health to discuss recent work in this area and to identify new areas of research. A summary of the proceedings has been published in the *Journal of Bone and Mineral Research* (Sharrock WJ. *J Bone Miner Res*, 1998;13:537-543).

Research Objectives and Scope

Appreciation of the complexity of the factors that may influence bone is still growing. Clearly, many potentially interacting cell types and participating effector molecules must be considered in interpreting laboratory results and clinical observations. Future efforts seem likely to be particularly rewarding if they can either clarify the importance of specific cell types and effector

molecules or identify previously unrecognized cellular and molecular agents that influence bone physiology. Important areas include, but are not limited to:

- o Determination of the mechanisms that regulate the differentiation of the stromal, osteoblastic, and osteoclastic lineages, including the nature of osteogenic stem cells and factors that govern the disposition of multipotential precursors among alternate pathways;
- o Identification of other marrow cell types, such as hematopoietic cells and stages of lymphoid and myeloid differentiation, that may influence bone cells;
- o Characterization of functional interactions between cell types present in the marrow;
- o Definition of homing of stem cells and hematopoietic precursors as a function of stromal and matrix environments;
- o Exploration of the possibility that cells of the stromal/osteogenic lineage circulate in the blood;
- o Determination of the mechanisms that underlie the organization of the marrow, including specific cell-cell associations and the role of extracellular matrix components;
- o Testing of the significance of hematopoietic and immune influences in the differentiation of intramembranous as opposed to endochondral bone;
- o Definition of the differences between currently used model systems, with attention to species and strain differences, properties of cells from different anatomical sites, and the characteristics of different in vitro systems;
- o Determination of the mechanisms underlying the skeletal effects of systemic factors, including sex steroids, PTH, and immunosuppressants, in terms of the roles of intermediary cells and signaling pathways;
- o Testing of the possible roles of circulating lymphocytes and other immune cells in normal and pathological bone metabolism;
- o Elucidation of the effect of osteopenia on hematopoiesis and of hematopoiesis on bone elements in normal and pathological states, such as myelodysplasia and aplastic anemia;

- o Study of the relationship between hematopoietic malignancies, such as myeloma, and pathological bone resorption;

- o Determination of the mechanisms through which these complex molecular and cellular interactions may be involved in bone loss in older subjects.

Collaborations among bone biologists, hematologists, and immunologists are encouraged, as they can be expected to enrich the available array of models and experimental systems. For example, many transgenic and knockout mouse strains have been developed to probe hematopoietic and immune regulatory mechanisms. In some cases, the phenotypes include well-defined changes in the numbers of specific cell types and levels of regulatory molecules that may have important effects on bone. Examination of skeletal status in these strains may be illuminating. It is also anticipated that the utilization of technology allowing cell type-specific gene inactivation and transgene expression should provide more narrowly focused probes of mechanisms affecting bone. Similarly, new in vitro systems may provide opportunities to test interactions in complex populations of cells.

Finally, because of the evident differences between humans and animals in several important areas, the coupling of cellular and molecular analyses with clinical observation and intervention is likely to be critical for future progress. Results from studies of the mechanisms of immunosuppressive drugs and the effects of genetic disorders suggest that human pathology can provide important clues to fundamental mechanisms. There may be gains to be realized from examining the skeleton in clinical situations in which disruptions of hematopoietic or immune functions exist.

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 is 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, Vol. 23, No. 11, March 18, 1994 available on the web at the following URL address: <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 the following URL address: <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. Program staff may also provide additional relevant information concerning the policy.

APPLICATION PROCEDURES

Applications are to be submitted on the grant application form PHS 398 (rev.4/98) and will be accepted for the standard application receipt dates, as indicated in the application kit. Application kits are available at most institutional offices of sponsored research. Forms may also be obtained 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), or at <http://www.nih.gov/grants/funding/phs398/phs398.html>.

For research project (R01) grants with total direct costs not exceeding \$250,000 per year, the modifications noted below are to be used with application form PHS 398 (rev. 4/98).

BUDGET INSTRUCTIONS

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 - Do not complete Form Page 4 of the PHS 398. It is not required and will not be accepted with the application

o BUDGET FOR THE ENTIRE PROPOSED PERIOD OF SUPPORT - Do not complete the categorical budget table on Form Page 5 of the PHS 398. It is not required and will not be accepted with the application.

o NARRATIVE BUDGET JUSTIFICATION - Use a Modular Grant Budget Narrative page.

(See <http://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.

o Under Personnel, List key project personnel, including their names, percent of effort, and roles on the project. No individual salary information should be provided.

For Consortium/Contractual costs, provide an estimate of total costs (direct plus facilities and administrative) for each year, each rounded to the nearest \$1,000. List the individuals/organizations with whom consortium or contractual arrangements have been made, the percent effort of key personnel, and the role on the project. Indicate whether the collaborating institution is foreign or domestic. The total cost for a consortium/contractual arrangement is included in the overall requested modular direct cost amount.

Provide an additional narrative budget justification for any variation in the number of modules requested.

o BIOGRAPHICAL SKETCH - The Biographical Sketch provides information used by reviewers in the assessment of each individual's qualifications for a specific role in the proposed project, as well as to evaluate the overall qualifications of the research team. A biographical sketch is required for all key personnel, following the instructions below. No more than three pages may be used for each person. A sample biographical sketch may be viewed at:

<http://www.nih.gov/grants/funding/modular/modular.htm>

- Complete the educational block at the top of the form page;
- List current position(s) and then previous positions;
- List selected peer-reviewed publications, with full citations;
- Provide information, including overall goals and responsibilities, on research projects ongoing or completed during the last three years.

o CHECKLIST - This page should be completed and submitted with the application. If the F&A rate agreement has been established, indicate the type of agreement and the date. It is important to identify all exclusions that were used in the calculation of the F&A costs for the initial budget period and all future budget years.

o The applicant should provide the name and phone number of the individual to contact concerning fiscal and administrative issues if additional information is necessary following the initial review.

Any applicant planning to submit an investigator-initiated new (type 1), competing continuation (type 2), competing supplement, or any amended/revised version of the preceding grant application types requesting \$500,000 or more in direct costs for any year is advised that he or she must contact the Institute or Center (IC) program staff before submitting the application, i.e., as plans for the study are being developed. Furthermore, the applicant must obtain agreement from the IC staff that the IC will accept the application for consideration for award. Finally, the applicant must identify, in a cover letter sent with the application, the staff member and Institute or Center who agreed to accept assignment of the application. This policy requires an applicant to obtain agreement for acceptance of both any such application and any such subsequent amendment. Refer to the NIH Guide for Grants and Contracts, March 20, 1998 at <http://www.nih.gov/grants/guide/notice-files/not98-030.html>.

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

Submit a signed, typewritten original of the application, including the Checklist, and five signed photocopies in one package to:

CENTER FOR SCIENTIFIC REVIEW
NATIONAL INSTITUTES OF HEALTH
6701 ROCKLEDGE DRIVE, ROOM 1040, MSC 7710
BETHESDA, MD 20892-7710
BETHESDA, MD 20817 (for express/courier service)

REVIEW CONSIDERATIONS

Applications will be assigned on the basis of established PHS referral guidelines. Applications will be evaluated for scientific and technical merit by an appropriate scientific review group convened in accordance with the standard NIH peer review procedures. As part of the initial merit review, all applications will receive a written critique and undergo a process in which only those applications deemed to have the highest scientific merit, generally the top half of applications under review, will be discussed, assigned a priority score, and receive a second level review by the appropriate national advisory council or board.

Review Criteria

The goals of NIH-supported research are to advance our understanding of biological systems, improve the control of disease, and enhance health. In the written comments reviewers will be asked to discuss the following aspects of the application in order to judge the likelihood that the proposed research will have a substantial impact on the pursuit of these goals. Each of these criteria will be addressed and considered in assigning the overall score, weighting them as appropriate for each application. Note that the application does not need to be strong in all categories to be judged likely to have major scientific impact and thus deserve a high priority score. For example, an investigator may propose to carry out important work that by its nature is not innovative but is essential to move a field forward.

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

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

(3) Innovation: Does the project employ novel concepts, approaches or method? Are the aims original and innovative? Does the project challenge existing paradigms or develop new methodologies or technologies?

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

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

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

- o The adequacy of plans to include both genders, minorities and their subgroups, and children as appropriate for the scientific goals of the research. Plans for the recruitment and retention of subjects will also be evaluated.
- o The reasonableness of the proposed budget and duration in relation to the proposed research
- o The adequacy of the proposed protection for humans, animals or the environment, to the extent they may be adversely affected by the project proposed in the application.

The initial review group will also examine the provisions for the protection of human subjects and the safety of the research environment.

AWARD CRITERIA

In addition to the participating Institutes, several other Institutes and Centers have interests that are relevant to this Announcement. Applications will be assigned for possible funding according to existing referral guidelines and will compete for available funds with all other approved applications. The following will be considered in making funding decisions: quality of the proposed project as determined by peer review, availability of funds, and program priority. If considered for funding by the NIAMS, applications that are responsive to this Program Announcement are candidates for discretionary funding, as described at <http://www.nih.gov/niams/grants/payline2.htm> .

INQUIRIES

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

Direct inquiries regarding programmatic issues to:

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AUTHORITY AND REGULATIONS

This program is described in the Catalog of Federal Domestic Assistance Nos. 93.846, 93.866, 93.121, 93.849, and 93.839. 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 Part 52 and 45 CFR Part 74. This program is not subject to the intergovernmental review requirements of Executive Order 12372 or Health Systems Agency review.

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

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