

RESEARCH ON TISSUE ENGINEERING

Release Date: December 4, 1998

PA NUMBER: PA-99-024

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National Institute of Arthritis and Musculoskeletal and Skin Diseases

National Institute on Aging

National Institute for Child Health and Human Development

National Institute of Dental and Craniofacial Research

National Institute on Deafness and Other Communication Disorders

National Institute of Diabetes, Digestive, and Kidney Diseases

National Institute of General Medical Sciences

National Institute of Mental Health

National Institute of Neurological Disorders and Stroke

National Heart, Lung, and Blood Institute

National Center for Research Resources

Letter of Intent Receipt Date: February 2, 1999

Application Receipt Date: March 16, 1999

PURPOSE

The National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), the National Institute on Aging (NIA), the National Institute for Child Health and Human Development (NICHD), the National Institute of Dental and Craniofacial Research (NIDCR), the National Institute on Deafness and Other Communication Disorders (NIDCD), the National Institute of Diabetes, Digestive, and Kidney Diseases (NIDDK), the National Institute of General Medical Sciences (NIGMS), the National Institute of Mental Health (NIMH), the National Institute of Neurological Disorders and Stroke (NINDS), the National Heart, Lung, and Blood Institute (NHLBI), and the National Center for Research Resources (NCRR) encourage investigator-initiated research grant applications to study tissue engineering. The purpose of this Tissue Engineering Program Announcement (PA) is to inform the scientific community of the NIH's interests, and to stimulate and foster a wide range of basic and translational studies to: (1) develop optimal materials/designs for matrices/scaffolds; (2) better understand how matrices/scaffolds interact

with cells and their surrounding tissues; (3) develop better animal models; and (4) validate and standardize the criteria for a successful repair/replacement of tissues and organs.

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 PA, Research on Tissue Engineering, is related to the priority area of chronic disabling conditions. Potential applicants may obtain a copy of "Healthy People 2000" (Full Report: Stock No. 017-001-00474-0 or Summary Report: Stock No. 017-001-00473-1) through the Superintendent of Documents, Government Printing Office, Washington, DC 20402- 9325 (telephone 202-512-1800).

ELIGIBILITY REQUIREMENTS

Applications may be submitted by foreign and domestic, 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. Applications from minority individuals, women, and persons with disabilities are encouraged.

MECHANISM OF SUPPORT

The mechanism of support will be the research project grant (R01). R01s may include requests for up to five years of support and have no direct cost cap. Responsibility for the planning, direction, and execution of the proposed project will be solely that of the applicant. Awards will be administered under NIH grants policy as stated in the NIH Grants Policy statement.

RESEARCH OBJECTIVES

Background

A large number of Americans suffer organ and tissue loss every year from accidents, birth defects, hereditary disorders, conditions and diseases. Improved understanding of biological processes holds promise for the development of new classes of biomaterials, polymers, and diagnostic and analytical reagents. New avenues of scientific inquiry can enable the development of novel technologies for tissue and organ replacement technologies that are designed to perform ideally in their respective biological environments. The field of tissue

engineering offers a multitude of applications for the use of such engineered tissues and organs to treat these situations of organ/tissue loss or dysfunction. These potential applications range broadly across all the human organ systems.

Tissue engineering integrates discoveries from biochemistry, cell and molecular biology, genetics, material science and biomedical engineering to produce innovative three dimensional composites having structure/function properties that can be used to either replace or correct damaged, missing, or poorly functioning components in living systems. In addition, this emerging technology can be used to introduce better functioning components. The material components themselves may be processed from naturally occurring materials, processed from synthetic materials, or a combination of these. Cellular and other biologic components may be added.

These material components are usually called matrices or scaffolds. The function of these matrices/scaffolds is to direct the growth of cells migrating from surrounding tissue or of cells seeded within these porous structures themselves. They provide a suitable substrate for cell attachment, proliferation, differentiated function, and cell migration. These matrices/scaffolds can be permanent or biodegradable (temporary). Although there are many biocompatible materials, which could potentially be used to construct matrices/scaffolds, a biodegradable material may be more desirable, since the role of these matrices/scaffolds is usually temporary. Many naturally and biosynthetic biodegradable polymers have been developed (e.g., collagen, poly alpha-hydroxyesters, and polyanhydrides), and others are currently under development.

Scope of Research Sought

Much remains to be known regarding optimal materials for, and design of, successful implanted matrices/scaffolds. How they interact with their biologic surroundings? How can we validate and standardize the criteria for a successful repair or replacement? Through the use of this PA, the sponsoring Institutes anticipate the receipt of a broad range of applications targeted, but not limited, to the following areas related to the use of matrices/scaffolds in tissue engineering:

Develop optimal materials/designs for matrices/scaffolds

- o Permanent versus biodegradable;
- o Optimal lifespan of scaffold or product;
- o Degradation products;
- o Biocompatibility;
- o Optimal geometry/architecture/composition;
- o Surface features (and how to modify them--i.e., biomimetics);

- o Role of surface features in biointegration;
- o Biomechanical characteristics; and
- o Reproducibility.

Understand how matrices/scaffolds interact with cells

- o Receptor/recognition interactions;
- o Cell-to-cell signaling;
- o Orientation of molecules at the cell surface;
- o Influences of biomechanical stress on cell/matrix function;
- o Effect of matrix/scaffold degradation products on cell function; and
- o Effects of age/gender on biomaterials biocompatibility and longevity.

Development of improved animal models

- o Correlate in vitro with in vivo responses of biomaterials;
- o Develop standardized and quantitative cellular, genetic, and metabolic response assays/protocols, including those for accelerated biocompatibility; and
- o Develop noninvasive/nondestructive assays of biomaterial performance, including imaging modalities.

Validate and standardize the criteria for a successful tissue/organ repair or replacement using histologic, biochemical, biomechanical, electrical, (and other) parameters

- o Bioimaging technologies such as computer-aided light and electron microscopes, magnetic resonance imaging, etc.;
- o Development of engineered protein-based probes that can be used for integrated microscopy and other biomarker technologies; and
- o Development of chemical sensors and other biosensors to monitor biomaterials performance.

No priority has been established among the research suggestions presented. Research applications are encouraged from all basic science disciplines pertinent to this area, as well as the various clinical specialties providing health care services to patients who may benefit from tissue engineering interventions.

INCLUSION OF WOMEN AND MINORITIES IN RESEARCH INVOLVING HUMAN SUBJECTS

It is the policy of 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 was published in the Federal Register on March 28, 1994 (FR 59 14508-14513) and in the NIH Guide for Grants and Contracts , Volume 23, Number 11, March 18, 1994. This information is available on the internet at <http://www.nih.gov/grants/guide/notice-files/not94-105.html>.

INCLUSION OF CHILDREN AS PARTICIPANTS IN RESEARCH INVOLVING HUMAN SUBJECTS

It is the policy of the NIH that children must be included in all human subject research conducted or supported by the NIH unless there are scientific or ethical reasons not to include them. The goal of the policy is to increase the participation of children in research to obtain appropriate data.

This policy applies to all initial (Type 1) applications submitted for receipt dates after October 1, 1998. The policy does not apply to ongoing studies (e.g., Type 5, Type 2) or previously reviewed amended applications. 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" which was published in the NIH Guide for Grants and Contracts, March 6, 1998. This information is available on the internet at <http://www.nih.gov/grants/guide/notice-files/not98-024.html>.

Investigators also may obtain copies of the policies on "Inclusion of Women and Minorities in Research Involving Human Subjects" and "Inclusion of Children as Participants in Research Involving Human Subjects" from the program staff listed under INQUIRIES. Program staff may also provide additional relevant information concerning the policy.

LETTER OF INTENT

Potential applicants are requested to submit, by February 2, 1999, a letter of intent that includes a descriptive title of the proposed research, the name, address, and telephone number of the principal investigator, the identities of other key personnel and participating institutions, and the number and title of this PA. The letter of intent is to be sent to Dr. James S. Panagis at the address listed under INQUIRIES.

APPLICATION PROCEDURES

Applications are to be submitted on the grant application form PHS 398 (rev.4/98). Application kits are available at most institutional offices of sponsored research and may 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. The title and number of the program announcement must be typed in Section 2 on the face page of the application.

Applicants planning to submit an investigator-initiated new (type 1), competing continuation (type 2), competing supplement, or any amended/revised version of the preceding grant application types requesting \$500,000 or more in direct costs for any year are advised that he or she must contact the Institute or Center (IC) program staff before submitting the application, i.e, as plans for the study are being developed. Furthermore, the application 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.

The completed original application and five legible copies must be sent or delivered 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 that are complete will be evaluated for scientific and technical merit by an appropriate peer review group convened in accordance with 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 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, and in accordance with NIH policy, all applications will also be reviewed with respect to the following:

(1) 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.

(2) The reasonableness of the proposed budget and duration in relation to the proposed research.

(3) 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 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.

INQUIRIES

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

Direct inquiries regarding programmatic issues to:

James S. Panagis, M.D., M.P.H.

Orthopaedics Program

National Institute of Arthritis and Musculoskeletal and Skin Diseases

45 Center Drive, Room 5AS-37K, MSC 4500

Bethesda, MD 20892-6500

Telephone: (301) 594-5055

FAX: (301) 480-4543

Email: jp149d@nih.gov

Alan Berson, Ph.D.

Division of Heart and Vascular Diseases

National Heart, Lung, and Blood Institute

6701 Rockledge Drive, Room 9182

Bethesda, MD 20892-7910

Telephone: (301) 435-0513

FAX: (301) 480-1454

Email: ab51@nih.gov

Chhanda Dutta, Ph.D.

Geriatrics Program

National Institute on Aging

7201 Wisconsin Avenue, Suite 3E-327, MSC 9205

Bethesda, MD 20892-9205

Telephone: (301) 435-3048

FAX: (301) 402-1784

Email: DuttaC@exmur.nia.nih.gov

Eleni Kousvelari, D.D.S., D.Sc.

Biomaterials, Biomimetics and Tissue Engineering Program

National Institute of Dental and Craniofacial Research

45 Center Drive, Room 4AN-18A, MSC 6500

Bethesda, MD 20892-6500

Telephone: (301) 594-2427

FAX: (301) 480-8318

Email: kousvelari@de45.nidr.nih.gov

Mary Ellen Cheung, Ph.D.

National Center for Medical Rehabilitation Research

National Institute of Child Health and Human Development

6100 Executive Boulevard, Room 2A03

Bethesda, MD 20852

Telephone: (301) 402-2242

FAX: (301) 402-0832

Email: mm108w@nih.gov

William Heetderks, M.D., Ph.D.

Division of Stroke, Trauma, and Neurodegenerative Disorders

National Institute for Neurological Disorders and Stroke

Federal Building, Room 8A13

Bethesda, MD 20892-9155

Telephone: (301) 496-1447

FAX: (301) 402-1501

Email: Heet@nih.gov

Lynn E. Huerta, PhD
Division of Human Communication
National Institute on Deafness and Other Communication Disorders
6120 Executive Boulevard, Room 400-C, MSC 7180
Bethesda, MD 20892-7180
Telephone: (301) 402-3458
FAX: (301) 402-6251
Email: Lynn_Huerta@nih.gov

Michael F. Huerta, Ph.D.
Division of Basic and Clinical Neuroscience Research
National Institute of Mental Health
5600 Fishers Lane, Room 11-103
Rockville, MD 20857
Telephone: (301) 443-3563
FAX: (301) 423-1731
Email: mhuerta@helix.nih.gov

Karl A. Koehler, Ph.D.
National Center for Research Resources
6705 Rockledge Drive, Room 6146, MSC 7965
Bethesda, MD 20892-7965
Telephone: (301) 435-0755
FAX: (301) 480-3775
Email: karlk@ep.ncrr.nih.gov

Ronald N. Margolis, Ph.D.
Senior Advisor for Molecular Endocrinology
National Institute of Diabetes, Digestive, and Kidney Diseases
45 Center Drive, Room 5AN-12J, MSC 6600
Bethesda, MD 20892-6600
Telephone: (301) 594-8819
FAX: (301) 435-6047
Email: rm76f@nih.gov

Michael E. Rogers, Ph.D.

Division of Pharmacology, Physiology and Biological Chemistry
National Institute of General Medical Sciences
45 Center Drive, MSC 6200
Bethesda, MD 20892-6200
Telephone: (301) 594-3827
FAX: (301) 480-2802
Email: rogersm@nigms.nih.gov

Direct inquiries regarding fiscal matters to:

Irene Grissom
Grants Management Branch
National Institute of Arthritis and Musculoskeletal and Skin Diseases
45 Center Drive, Room 5AS-43J, MSC 4500
Bethesda, MD 20892-6500
Telephone: (301) 594-3535
FAX: (301) 480-5450
Email: grissomi@mail.nih.gov

Bruce Butrum
Grants Operations Branch
National Heart, Lung, and Blood Institute
6701 Rockledge Drive, Room 7142
Bethesda, MD 20892
Telephone: (301) 435-0177
FAX: (301) 480-3310
Email: butrumb@gwgate.nhlbi.nih.gov

Mary Ellen Colvin
Grants Management Branch
National Institute of Child Health and Human Development
6100 Executive Boulevard, Room 8A17
Rockville, MD 20852
Telephone: (301) 496-1303
FAX: (301) 402-0915
Email: mc113b@nih.gov

Joseph Ellis
Grants and Contracts Management
National Institute on Aging
7201 Wisconsin Avenue, Suite 2N-212, MSC 9205
Bethesda, MD 20892-9205
Telephone: (301) 496-1472
FAX: (301) 402-3672
Email: EllisJ@exmur.nia.nih.gov

Toni Holland
Grants Management Office
National Institute of General Medical Sciences
45 Center Drive, Room 2AN-50-B, MSC 6200
Bethesda, MD 20892-6200
Telephone: (301) 594-5132
FAX: (301) 480-2554
Email: hollandat@nigms.nih.gov

Sharon Hunt
Grants Management Branch
National Institute on Deafness and other Communication Disorders
6120 Executive Boulevard, Room 400-C, MSC 7180
Bethesda, MD 20892-7180
Telephone: (301) 402-0909
FAX: (301) 402-1758
Email: sharon_hunt@nih.gov

Brenda Kibler
Grants Management Specialist
National Institute for Neurological Disorders and Stroke
Federal Building, Room 1004
Bethesda, MD 20892
Telephone: (301) 496-9231
FAX: (301) 402-0219
Email: bk29j@nih.gov

Ephraim Johnson

Grants Management Specialist
National Institute of Diabetes, Digestive, and Kidney Diseases
45 Center Drive, Room 6AN-44D, MSC 6600
Bethesda, MD 20892-6600
Telephone: (301) 594-8856
FAX: (301) 480-3504
Email: johnsone@extra.niddk.nih.gov

Judith D. Musgrave
National Center for Research Resources
Office of Grants Management
6705 Rockledge Drive, Room 6198, MSC 7965
Bethesda, MD 20892-7965
Telephone: (301) 435-0841
FAX: (301) 480-3777
Email: judithm@ep.ncrr.nih.gov

Martin Rubinstein
Grants Management Branch
National Institute of Dental and Craniofacial Research
45 Center Drive, Room 4AN-44A, MSC 6500
Bethesda, MD 20892-6500
Telephone: (301) 594-4800
FAX: (301) 480-8301
Email: mr49c@nih.gov

E. Douglas Shawver
Grants Management Branch
National Institute of Child Health and Human Development
6100 Executive Boulevard, Room 8A17, MSC 7510
Bethesda, MD 20892-7510
Telephone: (301) 496-1303
FAX: (301) 402-0915
Email: shawverd@exchange.nichd.nih.gov

Diana S. Trunnell
Grants Management Branch

National Institute of Mental Health
Parklawn Building, Room 7C-08
Rockville, MD 20857
Telephone: (301) 443-2805
FAX: (301) 443-6885
Email: Diana_Trunnell@nih.gov

AUTHORITY AND REGULATIONS

This program is described in the Catalog of Federal Domestic Assistance No. 93.846. Awards will be made under the authority of the Public Health Service Act, Title III, Section 301 (Public Law 410, 78th Congress, as amended, 42 USC 241) and administered under PHS grant policies and Federal regulations 42 CFR Part 52 and 45 CFR Part 74. This program is not subject to 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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