

NATIONAL SPACE BIOMEDICAL RESEARCH INSTITUTE

Research Announcement

**An Opportunity to Participate in the
Core Research Program of the
National Space Biomedical Research Institute**

Expansion of Current Research Teams

February 22, 2000

NSBRI 00-01

TABLE OF CONTENTS

1.0 OPPORTUNITY	1
2.0 BACKGROUND	2
2.1 Institute Infrastructure	2
2.2 Current Research Program.....	3
2.3 Planned Augmentation.....	4
3.0 SPECIFIC RESEARCH FOCUS	4
3.1 General Information.....	4
3.2 Bone Loss.....	5
3.3 Cardiovascular Alterations	11
3.4 Human Performance Factors, Sleep and Chronobiology.....	14
3.5 Immunology, Infection and Hematology	17
3.6 Muscle Alterations and Atrophy.....	20
3.7 Neurovestibular Adaptation.....	22
3.8 Radiation Effects	26
3.9 Technology Development	28

4.0 APPLICATION PROCEDURES 32
 4.1 General Instructions 32
 4.2 Special Instructions 32
5.0 COMPETITIVE PROCESS 34
 5.1 Review and Selection Process 34
 5.2 Evaluation and Award Criteria 35
6.0 SCHEDULE 36

TABLES

1. Countermeasure Readiness Levels 6
2. Team Leaders for the Current NSBRI Research Areas 7

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1.0 OPPORTUNITY

The National Space Biomedical Research Institute (NSBRI), a private, non-profit organization, invites research project applications for the support of ground-based and limited space flight research in eight *currently active* research areas:

- bone loss;
- cardiovascular alterations;
- human performance factors, sleep and chronobiology;
- immunology, infection and hematology;
- muscle alterations and atrophy;
- neurovestibular adaptation;
- radiation effects; and
- technology development.

The purpose of this announcement is to solicit research proposals from investigators wishing to serve as members of research teams pursuing coordinated programs of activity in each of these eight areas. Only investigators interested in becoming members of these eight teams should apply to this announcement. Another research announcement recruiting investigators to participate in four new NSBRI research areas was released in December 1999 and is available on the NSBRI web site (<http://www.nsbri.org/>).

Each of the eight research teams will consist of a set of individual coordinated and complementary projects focused on a common theme. Team management and coordination will be the responsibility of a program director called a Team Leader. The current Team Leaders for these eight teams are listed in Section 3 of this announcement.

Applications will be accepted from all categories of organizations, public and private, and for-profit and non-profit, such as universities, colleges, hospitals, laboratories, units of state and local governments, and eligible agencies of the Federal government. The mechanism of support shall be an NSBRI subagreement with funds provided by the National Aeronautics and Space Administration (NASA) through a cooperative agreement (Cooperative Agreement NCC 9-58 with NASA's Lyndon B. Johnson Space Center). Annual renewal awards are subject to an independent, external review. Potential foreign applicants should note that, normally, applications from non-U.S. organizations must be funded by the country of origin, not directly by the NSBRI.

Although space flight applications may be submitted in response to this announcement, potential applicants should be aware of the limited flight resources available during the time frame of support for flight investigations through this announcement and take those resources into account in preparing their proposal (see Section 4.2).

2.0 BACKGROUND

The NSBRI is responsible for the development of countermeasures against the deleterious effects of long-duration space flight and performs fundamental and applied space biomedical research directed towards this specific goal. Its mission is to lead a world-class, national effort in integrated, critical path space biomedical research that supports NASA's Human Exploration and Development of Space (HEDS) Strategic Plan by focusing on the enabling of long-term human presence in, development of, and exploration of space. This is accomplished by:

- designing, testing and validating effective countermeasures to address the biological and environmental impediments to long-term human space flight;
- defining the molecular, cellular, organ-level, integrated responses and mechanistic relationships that ultimately determine these impediments, where such activity fosters the development of novel countermeasures;
- establishing biomedical support technologies to maximize human performance in space, reduce biomedical hazards to an acceptable level, and deliver quality medical care;
- transferring and disseminating the biomedical advances in knowledge and technology acquired through living and working in space to the general benefit of mankind, including the treatment of patients suffering from gravity- and radiation-related conditions on Earth; and
- ensuring open involvement of the scientific community, industry and the public at large in the Institute's activities and fostering a robust collaboration with NASA, particularly through NASA's Lyndon B. Johnson Space Center.

The NSBRI was established in April 1997 following competitive selection by NASA. Primary support for the NSBRI's activities is furnished by NASA through a cooperative agreement although funds to support Institute activities also come from several sources, including the institutions involved in carrying out the NSBRI's programs. The cooperative agreement award is for a five and one-half year base period, lasting until September 30, 2002, and three five-year optional extensions. Current base funding has been set at approximately \$10 million annually. However, NASA has notified the Institute that it would like the NSBRI to expand its activities significantly and will provide additional funds during FY 2000 to develop the infrastructure to support planned program growth beginning in FY 2001. This solicitation is being issued in anticipation of a substantial increase in the NSBRI's core research budget beginning in October 2000, an increase that will require appropriate budgetary authorization and approval by the U.S. Congress. Prospective investigators should be aware that the implementation of the planned augmentation described in this announcement is contingent upon such favorable Congressional action.

2.1 Institute Infrastructure

The NSBRI is governed by a consortium of twelve institutions that includes Baylor College of Medicine, Brookhaven National Laboratory, Harvard Medical School, The Johns Hopkins University School of Medicine and the Applied Physics Laboratory, Massachusetts Institute of Technology, Morehouse School of Medicine, Mount Sinai School of Medicine, Rice University, Texas A&M University, the University of Arkansas for Medical Sciences, the University of Pennsylvania Health

System, and the University of Washington. The Institute's headquarters are located in Houston at Baylor College of Medicine.

Because of the nature of the competitive process used by NASA to select the NSBRI, most of the Institute's initial three-year research program is carried out at the consortium institutions. There are, however, no restrictions concerning institutional participation in Institute activity. In fact, the current program is carried out at more than twenty institutions and government laboratories in addition to the consortium. The management plan for the Institute is based on the model used by the National Institutes of Health. An independent Board of Scientific Counselors is responsible for assuring excellence in the Institute's intramural program through independent external peer review, and an External Advisory Council is responsible for advising Institute management concerning programmatic effectiveness. The NSBRI also has a User Panel of former and current astronauts and flight surgeons responsible for assuring that the research program is focused squarely on astronaut health and safety. An Industry Forum of representatives of space and biomedically-related industries assists the Institute in developing industry participation in NSBRI and in timely technology transfer. In addition to its research program, the NSBRI has developed a vital education and outreach program which takes advantage of the Institute's core research activities.

2.2 Current Research Program

The NSBRI's initial strategic research agenda involves eight teams of scientists focused on:

- *Bone Loss* – Addressing the loss and weakening of bone during space flight with the inherent fracture risks;
- *Cardiovascular Alterations* – Addressing the inflight increase of cardiac dysrhythmias and postflight impairment of the cardiovascular response to orthostatic and exercise stress;
- *Human Performance Factors, Sleep and Chronobiology* – Addressing maintenance of high cognitive performance and vigilance despite environmental stress and sleep disturbances;
- *Immunology, Infection and Hematology* – Addressing the potential for immune system impairment and altered susceptibility to infection, increased allergic response, decreased blood volume and postflight anemia;
- *Muscle Alterations and Atrophy* – Addressing the loss of skeletal muscle mass, strength and endurance that accompanies space flight;
- *Neurovestibular Adaptation* – Addressing the problems of space motion sickness and disorientation during flight and the postflight problems of balance and gaze disorders;
- *Radiation Effects* – Addressing the problem of increased cancer risk caused by the natural space radiation environment; and
- *Technology Development* – Developing instrumentation that will enhance the research of the other teams and transferring the technology to industry for the benefit of society.

Each research team consists of investigator groups working on complementary projects focused on a common theme. Team management and coordination is the responsibility of a program director called a Team Leader while overall scientific direction is the responsibility of the Institute Director and Associate Director. The total current intramural research program, including all eight research areas, involves 41 projects, with an average funding per project of approximately \$200,000 (Direct + Indirect Costs). Details concerning the current intramural projects and team leaders are provided on the web at: www.nsbri.org/research/newresearch.html.

In addition to this core intramural research program, the NSBRI has developed a joint program with the National Institute on Deafness and Other Communication Disorders (NIDCD) that

jointly funds six competitively-awarded extramural grants related to the dynamic adaptation of central vestibular function, an area of common interest. Finally, the NSBRI has begun to develop non-U.S. partnerships with the objective of enlarging the core research program by including projects carried out in other countries and supported by those countries. At this time, the Institute has signed an agreement of affiliation with the Institute of Aerospace Medicine of the German Aerospace Center in Cologne (Deutsches Zentrum für Luft- und Raumfahrt e.V., DLR), an agreement of cooperation with the Institute for Space Physiology and Medicine in Toulouse, France (Institut de Médecine et de Physiologie Spatiales, MEDES), and a framework agreement with the Politecnico di Milano. The NSBRI also has contractual relationships with the Russian Institute for Biomedical Problems in Moscow.

2.3 Planned Augmentation

On the basis of the Institute's initial successes, NASA and the NSBRI developed an augmentation plan that includes an increased number of research areas and intramural teams to allow for more complete coverage of the critical research problems of space biomedical research. It entails increased funding levels for all of the research areas and an augmented extramural grants program (the NSBRI-Federal Cooperative Program) based on the model program developed by the Institute with the NIDCD. In addition, the plan opens the opportunity to participate in the intramural team core research program to any member of the scientific community through the issuance of focused research solicitations. Finally, the augmentation plan will include the development of a small, nationally competitive graduate and postgraduate training program in space-related biomedical research and a significant enhancement to the current education and outreach program of the Institute. To carry out this plan, the Institute has already released an announcement to enlarge the NSBRI consortium (Announcement NSBRI 99-01, May 10, 1999) and has selected five new institutions to add to the consortium, bringing the membership to twelve. In addition, the Institute released a research announcement (Announcement NSBRI 99-02, December 28, 1999) to broaden the scope of Institute activity by forming four new research teams. The current research announcement (Announcement NSBRI 00-01) is being released to allow the eight original research teams to be enlarged.

3.0 SPECIFIC RESEARCH FOCUS

Proposals submitted in response to this announcement **MUST** address one of the eight research areas discussed below. Proposals for research that impacts more than one area should be directed to only one primary research area although a secondary research area may be mentioned for possible further review and consideration. The following subsections are meant to guide the investigator to the key problems and issues that are central to each of these research areas. Innovative approaches to the solution of these problems are encouraged.

3.1 General Information

To carry out the NSBRI's primary mission, that of designing, testing and validating effective countermeasures to address the biological and environmental impediments to human space flight (both within and beyond low-Earth orbit), the NSBRI focuses its research program on the needs of exploration-class space missions. These missions pose the greatest challenge to future space travelers, and meeting their challenge with appropriate countermeasures lies at the core of the NSBRI's responsibility. For planing purposes, a typical Mars-type exploration mission might involve trips of six months to one year each way, with a stay on Mars of one to two years. Effec-

tive adaptation, supported by appropriate countermeasures, is critical to a successful mission and to the long-term health maintenance of the astronauts. Potential physiological changes that may occur during prolonged space flight include, among others, significant loss of muscle and bone mass, decreased dietary intake of nutrients, profound metabolic and endocrine alterations, important changes in cardiovascular function and deleterious effects on sensorimotor performance. By addressing long-term missions of this type, increased safety, health and performance will be realized for shorter duration space flights.

Critical Path Roadmap. NASA and the NSBRI have begun jointly to develop a research plan aimed at reducing the biomedical risks of exploration-class missions. Included in this plan is a list of the major human risks involved in such missions and a set of critical research questions associated with those risks. For example, in the radiation research area, the primary risks that have been identified include damage to the central nervous system and carcinoma due to cosmic ray particles and ionizing radiation. A complete list of the exploration-mission risks and the associated critical questions may be found through a NASA web site (criticalpath.jsc.nasa.gov/). Investigators interested in responding to this announcement should become familiar with these risks and critical questions before preparing their final research plan. In addition, potential applicants should review the 1998 report by the National Research Council's Committee on Space Biology and Medicine entitled *A Strategy for Research in Space Biology and Medicine into the Next Century* (www.nap.edu/catalog/6282.html).

Countermeasure Readiness Levels. Since the NSBRI's primary mission concerns countermeasures, it is important to understand some of the steps involved in effective countermeasure development. These steps are called countermeasure readiness levels and are measured on a scale of 1 to 9, with the higher numbers referring to higher levels of readiness. As Table 1 shows, countermeasure development begins with basic research (levels 1 to 3), moves through countermeasure feasibility and development studies (levels 4 to 6), and ends with countermeasure ground evaluation, flight validation and operational implementation (levels 7 to 9). It is expected that the NSBRI's research program will contain studies ranging from level 2 through level 8, with most tasks ranging from level 3 through level 7.

3.2 Bone Loss

Team Leader: Jay R. Shapiro, M.D.
Uniformed Services University of the Health Sciences
(See Table 2)

Although bone loss has been an important problem since the Skylab flights of the early 1970's, it is only with the advent of extended-duration flights in the Russian Mir program and the availability of increasingly accurate measurements of bone mass in the spine and hip, that the true extent of skeletal loss following prolonged microgravity exposure has been appreciated. Data from Russian and U.S. studies indicate that bone loss proceeds at an average rate of 1-2% per month with a wide range of maximal regional changes, ranging from no loss to as much as 20% loss at specific sites. Although the pattern and extent of bone loss during a prolonged exploration flight can only be estimated, the risks to a flight crew from fracture, soft tissue injury and renal calculus formation constitute real hazards that must be minimized. In addition, another important crew health issue involves the rate of return to baseline bone mass with intact soft tissue integrity

Table 1. COUNTERMEASURE READINESS LEVELS

BASIC RESEARCH		1. PHENOMENON OBSERVED AND REPORTED, PROBLEM DEFINED.
	—	2. HYPOTHESIS FORMED, PRELIMINARY STUDIES TO DEFINE PARAMETERS, DEMONSTRATE FEASIBILITY.
RESEARCH TO PROVE FEASIBILITY		3. VALIDATED HYPOTHESIS, UNDERSTANDING OF SCIENTIFIC PROCESSES UNDERLYING PROBLEM.
		4. FORMULATION OF COUNTERMEASURES CONCEPT, BASED ON UNDERSTANDING OF PHENOMENON.
COUNTERMEASURE DEVELOPMENT		5. PROOF OF CONCEPT TESTING AND INITIAL DEMONSTRATION OF FEASIBILITY AND EFFICACY.
	—	6. LABORATORY/CLINICAL TESTING OF POTENTIAL COUNTERMEASURE IN HUMAN SUBJECTS TO DEMONSTRATE EFFICACY OF CONCEPT FOR SPECIFIC PROBLEM.
COUNTERMEASURE DEMONSTRATION		7. INTEGRATED EVALUATION WITH HUMAN SUBJECTS IN CONTROLLED LABORATORY CONDITIONS SIMULATING OPERATIONAL SPACE FLIGHT ENVIRONMENT.
	—	8. VALIDATION WITH HUMAN SUBJECTS IN ACTUAL OPERATIONAL SPACE FLIGHT TO DEMONSTRATE EFFICACY AND OPERATIONAL FEASIBILITY.
COUNTERMEASURE OPERATIONS	—	9. COUNTERMEASURE FULLY FLIGHT TESTED AND READY FOR OPERATIONAL IMPLEMENTATION.

Table 2. Team Leaders for the Current NSBRI Research Areas

<p>Bone Loss Jay R. Shapiro, M.D. Walter Reed Army Medical Center Building 2 Ward 64, Rm. 6433 Washington, DC 20307-5001 202-782-8933 202-782-3539 FAX Jay.Shapiro@NA.AMEDD.ARMY.MIL</p>	<p>Cardiovascular Alterations Richard J. Cohen, M.D., Ph.D. Harvard-MIT Division of Health Sciences and Technology Massachusetts Institute of Technology 77 Massachusetts Avenue Room E25-335a Cambridge, MA 02139 617-253-7430 617-253-3019 FAX rjcohen@mit.edu</p>
<p>Human Performance Factors ... Charles A. Czeisler, M.D., Ph.D. Brigham and Women's Hospital Harvard Medical School 221 Longwood Avenue, Suite 438A Boston, MA 02115 617-732-4011, ext. 4013 617-732-4015 FAX caczeisler@gcrc.bwh.harvard.edu</p>	<p>Immunology, Infection and Hematology William T. Shearer, M.D., Ph.D. Baylor College of Medicine 6621 Fannin, MC 1-3291 Houston, TX 77030 713-770-1274 713-770-7131 FAX wshearer@bcm.tmc.edu</p>
<p>Muscle Alterations and Atrophy</p>	
<p>Susan Hamilton, Ph.D. Baylor College of Medicine, BCMA 429E Houston, TX 77030 713-798-3894 713-798-5441 FAX susanh@bcm.tmc.edu</p>	<p>Robert J. Schwartz, Ph.D. Baylor College of Medicine One Baylor Plaza, BCMC 145EA Houston, TX 77030 713-798-6649 713-798-7799 FAX schwartz@bcm.tmc.edu</p>
<p>Neurovestibular Adaptation Charles M. Oman, Ph.D. Massachusetts Institute of Technology 77 Massachusetts Avenue Room 37-219 Cambridge, MA 02139 617-253-7508 617-253-0861 FAX cmo@space.mit.edu</p>	<p>Radiation Effects John F. Dicello, Ph.D. Johns Hopkins University School of Medicine 600 North Wolfe Street Room B1-170 Baltimore, MD 21287-8922 410-614-4194 410-955-3691 FAX diceljo@jhmi.edu</p>
<p>Technology Development Vincent L. Pisacane, Ph.D. Johns Hopkins University Applied Physics Laboratory 11100 Johns Hopkins Road Laurel, MD 20723-6099 443-778-5100 443-778-5995 FAX vince.pisacane@jhuapl.edu</p>	

following the return to Earth's gravity. The Critical Path Roadmap (see Section 3.1) has identified four major bone/connective tissue complications that derive from extended space flight: (1) the development of osteoporosis, (2) enhanced fracture risk and delayed fracture healing, (3) soft tissue injury, and (4) renal calculus formation.

The Bone Loss Team has as its main objectives the development and testing of *countermeasures* to protect astronauts against the above hazards. In considering the design of research projects, applicants should be aware that opportunities for inflight testing of novel countermeasures in animals or humans during the period of this funding cycle are very limited. Therefore, consideration should be given to projects that are primarily designed for initial testing on Earth. In spite of this, research protocols aimed at the development and testing of *operational* countermeasures are strongly encouraged. Developing a basic scientific understanding of the way that microgravity directly and indirectly effects bone, soft tissues and the kidney is key to effective countermeasure development. Thus, the submission of *mechanistic* studies is also strongly encouraged, with the proviso that these be focused on the later development of operational countermeasures that would eventually be tested during space flight.

Within this research area, the following eight interrelated themes define the scope of activities of interest:

- A. **Definition of factors related to maintaining normal bone mass during extended space flight and extraterrestrial habitation.** An important component of this theme is the preflight assessment of the potential for bone loss (baseline bone mass, bone structure and geometry, bone strength, and the genetic influences on the rate of bone loss). In addition, alterations in the mechanical strain environment and in the hormonal environment influence the maintenance of bone mass by impacting mechanisms affecting bone cell biology during exposure to microgravity.
- B. **Development of operational countermeasures to bone loss.** These include biomechanical, pharmacologic, nutritional, environmental or other interventions designed to minimize bone loss and reduce the risk of fracture. This theme includes the development of methods to assess the efficacy of countermeasures on bone mineral density and strength and on the structural quality of bone.
- C. **Understanding the mechanisms that retard the return of bone mass to preflight levels and the development of countermeasures or specific rehabilitation strategies to promote regaining preflight bone strength.** The mechanisms that retard the response of bone on re-exposure to Earth's gravity are currently undefined. The development of operational countermeasures to minimize fracture risk after return from extended duration space flight is of high priority.
- D. **Assessment of fracture risk and the cellular/molecular mechanisms involved in fracture healing.** This theme requires the development of countermeasures (pharmacologic, biophysical, hormonal or nutritional) to promote normal fracture healing in a hypogravity environment. It also includes how microgravity influences the cellular processes involved in fracture healing, the rate of fracture healing and the quality of bone produced. An important issue is the development of suitable animal models to study fracture healing on Earth and during flight
- E. **Assessment of the impact of microgravity on the cellular and molecular biology of skeletal and supporting connective tissues.** This theme addresses microgravity-induced changes that lead to a reduction in the quantity, quality and structural integrity of bone and connective tissues. The effects of alterations in mechanical strain and pharmacologic agents on cell structure and function are important components. This includes the development of high throughput models for testing countermeasures including the use of

- cDNA microarrays and differential mRNA displays to study gene expression. These applications may help define new drug targets for countermeasure development.
- F. **Understanding muscle/bone interactions.** Understanding microgravity effects on muscle/bone interactions are critical to the development of effective countermeasures. This theme includes the responses of bone and bone-cell populations to progressive muscle atrophy. The regulatory components transducing the effects of mechanical strain on bone also must be defined.
- G. **Effects of microgravity on the integrity of supporting connective tissues.** This theme is concerned with the identification and assessment of the extent of injury to intervertebral discs, articular cartilage, meniscus, ligaments and tendons during and after periods of microgravity. Also of concern is how tissue injury inflight predisposes to postflight complications such as osteoarthritis and disc degeneration.
- H. **Minimizing the risk of renal calculus formation.** The risk of renal calculus formation is largely a consequence of increased bone resorption and decreased renal calcium reabsorption. Other microgravity-induced alterations of the urinary environment may increase the propensity to stone formation. Of interest are hypogravity's effect on renal function, the excretion of urinary macromolecular inhibitors/promoters of crystallization environment and nutritional contributions to altered urinary composition. The design of countermeasures should include methods for decreasing the urinary concentration of stone-forming constituents while improving crystallization inhibitory activity.

Research Questions

The preceding themes are associated with a broad range of research questions. For convenience, these have been organized below within five categories. It is emphasized that these topics are intended to focus research efforts on the development of testable and effective countermeasures to skeletal/connective alterations related to human exposure to microgravity.

Prevention of Microgravity-Induced Osteoporosis

- What are the microgravity-induced cellular and molecular changes that lead to reduction in bone quantity and quality?
- What mechanisms underlie the hormonal changes (e.g., PTH, 25(OH)D, 1,25(OH)D₂, etc.) during space flight and chronic bed rest?
- What are the important predictors of fracture risk, including ethnicity, gender, bone mineral density, bone biomarkers and bone structural properties?
- Which Earth-based models simulating microgravity are best suited for evaluating countermeasures to bone loss in humans?
- What parameters of mechanical strain (e.g., frequency, intensity, duration) and/or exercise (e.g., mode) influence bone and connective tissues?
- Which nutritional or pharmacologic interventions, together with other modalities (e.g., exercise), best preserve skeletal integrity during exposure to hypogravity?
- How does space flight compromise the interdependence of the neuromuscular and skeletal systems, and to what degree can this be prevented?
- What instrumentation will best predict sequential changes in bone quality and quantity during space flight?

Fracture Risk and Fracture Healing

- Is fracture healing impaired in microgravity?
- Which animal models are best for observing the processes of fracture healing and callus formation in a simulated microgravity environment or during space flight?
- What are the effects of age, gender and race on fracture healing?
- What are the alterations in gene expression during fracture healing in the microgravity environment?
- What is the impact of environmental factors (e.g., sleep, cabin pressure, atmosphere composition) on fracture healing?
- What are the effects of mechanical influences such as fracture immobilization and electrical stimulation on fracture healing?
- What are the effects of growth factors and cytokines on fracture healing?
- Can methods of dynamic modeling be utilized to estimate the long-range effect of prolonged space flight on fracture risk?
- What countermeasures will best accelerate fracture healing in microgravity?

Microgravity and the Cell Biology of Skeletal and Supporting Connective Tissues

- By which mechanisms do bone and cartilage cells (periosteal cells, osteoblasts, osteocytes, osteoclasts and chondrocytes) sense and respond to alterations in gravity?
- How is cell-to-cell communication influenced by microgravity?
- What is cell life span in microgravity?
- What is the importance of apoptosis in modulating the bone's ability to respond to alterations in gravitational force?
- What are the microgravity effects on the maturation of osteoblast and osteoclast precursor cell populations in bone marrow and peripheral blood?
- How will countermeasures influence the processes of bone matrix synthesis, bone resorption and the maintenance of cartilage integrity under microgravity conditions?

Influence of Space Flight on Soft Tissues (Connective Tissues and Cartilage)

- What changes occur in the biology of soft tissue cells *in vitro* and *in vivo* under conditions that simulate aspects of space flight?
- What alterations occur in the molecular composition, microstructure and mechanical properties of the extracellular matrix during space flight?
- To what extent are cellular and extracellular matrix changes occurring during space flight reversible, or compensated for, by postflight therapies? To what extent can these changes be reduced by preflight treatment?
- To what extent are treatment protocols directed at preserving bone also effective in protecting soft tissues?
- How does space flight affect the response of soft tissues to injury and the activation of reparative processes?
- What developments will provide improved diagnostic markers for cartilage degradation and repair?

Renal Stone Formation

- What are the microgravity-induced alterations in serum components, urine formation and urine composition that increase the stone formation risk?
- Are there alterations in the hypothalamic-pituitary renal regulation of salt mineral and water excretion under microgravity conditions that promote kidney stone formation?
- What are the microgravity-induced alterations in urinary macromolecular inhibitors/promoters of stone formation? What is their contribution to risk for stone formation?
- Can nutritional alterations decrease the stone formation risk during space flight?
- Are there effective pharmacologic countermeasures that reduce stone formation risk?
- Can methods be developed for inflight monitoring of stone formation risk?

3.3 Cardiovascular Alterations

Team Leader: Richard J. Cohen, M.D., Ph.D.
Massachusetts Institute of Technology
(See Table 2)

During space flight, the cardiovascular system undergoes adaptive changes in structure and function in response to microgravity and other flight-related factors. While these adaptations appear to be associated with generally adequate cardiovascular performance during short-duration space flight, they are not appropriate upon reentry into a gravitational environment. The extent of cardiovascular adaptation appears to increase with the duration of space flight; however, the extent and implications of these adaptations for long-duration (months to years) space flight remain largely unknown. Space flight is associated with a movement of fluid from the lower extremity to the thorax and head, a modest decrease in intravascular volume, and a modest decrease in arterial pressure. During space flight, the cardiovascular system is not subjected to the stresses associated with changes in posture in a gravitational field. Other physiologic stressors, in addition to microgravity, such as sleep disruption, confinement and other environmental alterations, may adversely affect cardiovascular structure and function. Long-duration space flight leads to the development of orthostatic intolerance upon reentry into a gravitational field, may cause a reduction in cardiac mass, and might alter susceptibility to heart rhythm disturbances. In addition, long-duration space flight affects cardiovascular response to exercise and may, in principle, lead to the manifestation of previously asymptomatic cardiovascular diseases.

The objectives of the Cardiovascular Alterations Team are to: characterize and quantify the adverse effects of space flight on cardiovascular structure and function; determine the mechanisms of these effects; and develop effective countermeasures to reduce these adverse effects to an acceptable level. Proposed research projects may focus on one or more of these three objectives, but applicants should bear in mind that the ultimate goal of the research program is the development of countermeasures to mitigate the adverse effects of space flight on the cardiovascular system.

Research Questions

The research program of the Cardiovascular Alterations Team is driven by the critical risks identified through the Critical Path Roadmap (see Section 3.1). The cardiovascular risks are summarized below, together with some of the research questions whose resolution may lead to mitigation of those risks. The first three risks listed below are accorded the highest research

priority, and the last two are given a lower priority. Research proposed should be directed toward the goal of mitigating one or more of these cardiovascular risks in the most effective way. A number of cross-cutting issues, methods and approaches which may be relevant to the proposed research studies are listed following the five risks.

Impaired Cardiovascular Response to Orthostatic Stress. Upon reentry into the Earth's gravitational field, astronauts experience orthostatic intolerance that limits their ability to function during reentry and after landing. In many cases, the orthostatic intolerance is sufficiently severe that astronauts cannot stand erect for some time after landing. Upon reentry into a gravitational field, blood pools in the dependent arteries and veins which leads to a reduction in the preload to the heart, resulting in a decrease in stroke volume, cardiac output and arterial blood pressure. Factors that may be involved in the development of orthostatic intolerance include structural and functional adaptations of the heart and blood vessels, alterations in volume control mechanisms, alterations leading to an inadequate or defective neural and hormonal regulatory response, alterations in local vascular reactivity, and mechanisms controlling the regional distribution of blood volumes and flows. Orthostatic intolerance represents a current operational problem that may interfere with the astronaut's ability to egress from the spacecraft under emergency conditions, and is a substantial issue with regard to an astronaut's ability to function following a landing on Mars which has a gravitational field 3/8 of that found on Earth. Currently used countermeasures include oral administration of salt and water prior to reentry and application of anti-gravity suits; these countermeasures are not adequate to prevent orthostatic intolerance following long-duration space flight. Investigations elucidating the mechanisms involved in the development of orthostatic intolerance and determining their relative importance are encouraged. In addition, the study of mechanism-based interventions that may serve as countermeasures are particularly encouraged. Studies involving the investigation of factors that affect individual susceptibility to the development of postflight orthostatic intolerance are needed. Such factors may include age, gender and genotype, as well as occupational, physical training and dietary history.

Cardiac Atrophy and Remodeling. Long-term space flight may lead to a measurable reduction in cardiac mass. It is believed that this loss of cardiac mass is associated with cardiac remodeling. It is not known whether these cardiac alterations are reversible and whether they pose a long-term health risk to astronauts. The extent to which cardiac atrophy and remodeling may affect cardiac performance during long-duration space flight is inadequately understood. Furthermore, the detailed mechanisms involved in these changes remain to be elucidated. Research objectives include: quantification of changes in myocyte number, size and geometry; characterization of changes in myocardial matrix and microvasculature; characterization of alterations in myocyte and organ-level mechanical performance; characterization of changes in cardiac gene programming; study of the reversibility and recovery from these alterations; and identification of stimuli and signals that lead to loss of cardiac mass and remodeling. Identification of countermeasures that may prevent these alterations is particularly encouraged.

Occurrence of Serious Cardiac Dysrhythmias. Relatively little data are available on the association of space flight, and in particular long-duration space flight, with the development of heart rhythm disturbances. Anecdotal reports, including one documented 14-beat run of ventricular tachycardia during a Mir mission, suggest that long-duration space flight might lead to an increased incidence of potentially serious heart rhythm disturbances. However, data are currently inadequate to determine whether space flight predisposes the heart to rhythm disturbances. If space flight does significantly decrease cardiac electrical stability, the effects could be catastrophic, potentially leading to sudden cardiac death. In this area, the overriding research

question is whether space flight does increase susceptibility to cardiac dysrhythmias. If space flight is found to increase the risk of cardiac dysrhythmias, then it will be important to determine the mechanisms by which this occurs in order to develop appropriate countermeasures. Potential mechanisms that might lead to a reduction in the stability of the electrical substrate include electrolyte changes, changes in the neural and hormonal milieu, and alterations of cardiac myocytes, myocyte connectivity and extracellular matrix resulting from space flight. Approaches to ascertaining whether space flight might increase susceptibility to serious heart rhythm disturbances may include determining whether changes in cardiac conduction and repolarization that predispose to sustained rhythm disturbances occur in the context of appropriate space flight models or during space flight itself.

Manifestation of Previously Asymptomatic Cardiovascular Disease. Long-duration space flight may exacerbate previously undetected cardiovascular disease such as coronary artery disease. This area has been assigned a lower research priority than the preceding ones. However, research is needed to determine what procedures should be applied to screen astronauts for asymptomatic cardiovascular disease prior to long-term missions, such as a mission to Mars.

Impaired Cardiovascular Response to Exercise Stress. Long-term space flight may impair cardiovascular response to exercise. However, inflight exercise programs appear adequate to maintain aerobic exercise capacity. This research area is also assigned a lower research priority than the first three areas. In spite of this, research is needed to determine the type, duration and frequency of exercise necessary to maintain cardiovascular system integrity and, potentially, to prevent cardiac atrophy, and to determine whether thermoregulation is impaired during exercise.

Methods, Approaches and Cross-Cutting Issues

- **Experimental Models.** Proposed experimental studies may include ground-based animal or human studies, and space flight studies. As stated in Section 4.2, opportunities for space flight studies are limited. Because of this limitation, the great majority of experimental cardiovascular research in this area involves animal or human ground-based models of space flight. One question that arises is the extent to which these ground-based models yield results that correspond to space flight. To help validate these models, data available from space flight studies should be used to evaluate the degree of correspondence with data from ground-based models.
- **Experimental Approaches.** Studies may appropriately involve investigations ranging from the molecular, genetic and cellular level to the organ system level to the entire organism. Studies may include analysis of cardiovascular structure and function, investigation of cardiovascular regulation by local, neural and hormonal mechanisms, and nutritional investigations.
- **Mathematical and Computer Models.** Space flight causes alterations in multiple interacting physiologic systems. The use of mathematical and computer models to elucidate mechanisms, interpret data, and formulate hypotheses to be tested experimentally is encouraged. Such models may include forward models that simulate integrated physiologic behavior or inverse models used to create an individualized model of physiologic function from data recorded on a single individual. Both long-term and short-term phenomena may be analyzed over a variety of length scales from cell to whole organ system.
- **Conditions of Space Flight.** In addition to microgravity, other conditions of space flight,

including sleep disruption, reduced physical stress, environmental factors and psycho-social stresses, may also adversely affect the cardiovascular system.

- **Non-invasive Physiologic Measurement Techniques.** Non-invasive methods for studying the cardiovascular system are needed to help answer research questions and to serve as a means for monitoring astronaut cardiovascular function. Studies that appropriately utilize new, non-invasive (or minimally invasive) measurement techniques are encouraged.
- **Countermeasure Evaluation.** The development of countermeasures should be based on an understanding of the underlying physiologic mechanisms and might include genetic interventions in animal models as proof of concept. Translational research, based on mechanism-based interventions that may serve as countermeasures, is particularly encouraged. Countermeasures may include pharmacological, nutritional and physical interventions (including artificial gravity) and modifications of behavior, activity and environment.
- **Individual Susceptibility.** Investigation of factors that make an individual more susceptible to the adverse effects of space flight on the cardiovascular system may include age, gender, genotype and dietary, occupational and physical-conditioning history.
- **Cardiovascular Rehabilitation.** The adverse effects of space flight may persist following re-entry into a gravitational field. Identification of appropriate strategies for short-term and long-term cardiovascular rehabilitation is needed.
- **Earth Benefits.** Studies of the adverse effects of space flight on the cardiovascular system may also have important implications for clinical medicine issues on earth. Studies which may lead to such benefits are particularly encouraged.

3.4 Human Performance Factors, Sleep and Chronobiology

Team Leader: Charles A. Czeisler, M.D., Ph.D.
Harvard Medical School
(See Table 2)

The success of human space missions depends on each astronaut remaining alert and vigilant while operating sophisticated equipment and procedures. During long-duration space flight, the space environment affects those physiological systems critically involved in human performance, and it is vital to mission success to understand the biological limits of human performance under space flight conditions. This team is focused on these issues and, in particular, is concerned with the following aspects of the space environment: microgravity, altered light-dark cycles, altered or reduced sleep/rest opportunities, high levels of automation, and habitation in a remote, inaccessible location. The primary thrust of this team's research program involves altered circadian organization, sleep disruption and cumulative sleep loss, and the associated neurobehavioral decrements occurring during long-duration space flight.

The goals of the Human Performance Factors, Sleep and Chronobiology Team are to understand the basic mechanisms underlying the deterioration of sleep, circadian organization and human neurobehavioral function during space flight and to develop effective countermeasures based on understood mechanisms to optimize sleep, circadian organization and human neurobehavioral function in long-duration space flight. The overall team strategy is described in detail elsewhere (see the web site <http://www.nsbri.org/>). It includes the following objectives: to assess and

monitor the effects of long duration space flight on sleep, circadian rhythms and human performance; to investigate the mechanisms underlying sleep loss and circadian dysfunction and associated neurobehavioral performance decrements; to develop and validate predictive models for the effects of the space environment and associated sleep and circadian disruption on neurobehavioral performance; and to develop and validate countermeasures to ameliorate performance impairments.

Within this area of research, the following five interrelated themes define the range of factors critical for optimizing human performance capability and improving crew health and safety:

- A. Effects of long-duration space flight on sleep and/or circadian rhythmicity.** This theme addresses the impact of the conditions of long-duration space flight (microgravity, altered light intensity, loss of geophysical cues, isolation, altered physical activity, etc.) on neurobiologic, endocrinological, and behavioral mechanisms (molecular, cellular and organismic) that control sleep and circadian systems.
- B. Effects of sleep loss and/or circadian dysfunction on physical and neurobehavioral performance.** The focus of this theme is to identify the range of acute and chronic adverse effects that sleep loss, sleep disruption, and/or circadian dysfunction have on critical physiologic and performance parameters during long-duration space flight (e.g., neurophysiologic function, physiological alertness, vigilance, cognitive performance, mood/morale, problem solving and communication).
- C. Monitoring and assessment during space flight.** This theme deals with the development of methods for monitoring the status of sleep, sleep homeostasis and circadian organization, as well as technologies that assess and update the current functional status or performance capability of the individual.
- D. Predictive modeling of performance based upon circadian organization and sleep homeostasis.** This theme is concerned with the development of analytical or phenomenological mathematical models that predict individual human performance capability by involving multiple subsystems (e.g., circadian rhythmicity, sleep homeostasis, work-rest schedules, etc.) as an integrated unit across levels of organization, and by estimating the impact of countermeasure use designed to optimize human physical and/or neurobehavioral performance.
- E. Countermeasures.** The research program of this team will not only define the impact of the space environment on sleep and circadian rhythmicity and the effects of the sleep loss and circadian dysfunction on performance but also will develop methods to counter the adverse physiological and behavioral events. These countermeasures may include behavioral, pharmacological, environmental or other adaptive approaches to maintain function and performance under the adverse conditions of long-duration space flight.

Research Questions

The following questions are provided to assist the applicant in developing a proposal that is focused on relevant research. They are not complete, and project proposals may address other questions fitting within the programmatic interests defined above.

- What are the acute and long-term effects of extended duration space missions on biological rhythmicity and sleep, and what is the relationship of these effects to physical and neurobehavioral performance?
- How does space flight or exposure to chronic sleep restriction and/or circadian disruption affect sleep- and circadian-mediated neuroendocrine and autonomic functions, particularly

those relevant to risk mitigation (e.g., growth factors, glucocorticoids, monoamines) during extended-duration missions?

- What is the impact of space flight conditions (e.g., microgravity, altered light exposure and vestibular input, etc.) on the neurobiologic mechanisms (identified at either the cellular, molecular or organismic levels) of sleep-wake regulation, biological rhythmicity and coupling between these and other regulatory functions?
- How can performance during prolonged space flight be optimized by manipulating the neurobiologic processes underlying sleep and/or circadian rhythmicity?
- How do age and gender alter sleep- and circadian-mediated physiologic responses to, and risk mitigation for, prolonged space flight?
- To what extent can the fatigue observed following space flight be due to sleep loss, circadian misalignment, vestibular changes, performance demands or other factors associated with the transition from microgravity to a gravitational environment?
- Do the changes in sleep and/or circadian rhythmicity (e.g., partial chronic sleep deprivation, misalignment of circadian phase) observed during prolonged space flight lead to increased vulnerability to unanticipated operational demands?
- How do environmental factors, such as noise, temperature and/or the intensity and spectral distribution of light, cause or interact with sleep loss and/or circadian disruption to impair neurobehavioral performance?
- What are the appropriate biological model systems for the development and evaluation of countermeasures for sleep and/or circadian rhythm adjustment to long-duration space flight?
- How do task characteristics; operator environments; human-machine interactions; daily, weekly and long-term work-rest schedules; and recovery sleep/naps alter the effects of sleep loss and/or circadian disruption on human performance?
- What are the best methods, in terms of sensitivity and specificity, for monitoring the ongoing status of sleep, sleep homeostasis, circadian regulation and individual performance capability during extended duration space flight?
- How can methods for monitoring and assessment of performance capability during long-duration space flight be effectively implemented given the constraints of space flight (e.g., lack of privacy, transmission delay between the spacecraft and the ground station, etc.)?
- What mathematical models of sleep homeostasis and circadian regulation can effectively predict performance vulnerabilities in individuals subjected to prolonged space flight?
- How can mathematical models of sleep homeostasis and circadian regulation be used to provide guidelines for development and successful implementation of countermeasure strategies?
- How can mathematical and/or empirical models of sleep homeostasis and circadian regulation be used to design improved work-rest and task schedules?
- What measures of sleep, sleep disorders or circadian function predict individual neurobehavioral performance, adaptation or countermeasure efficacy? How can the identification of these parameters be used to facilitate successful adaptation to space flight?
- What are the effects of space flight on the pharmacokinetics, efficacy, side effects and interactions (drug-drug, drug-sleep, drug-circadian) of therapeutic agents designed to improve sleep, circadian regulation, and performance?
- Which behavioral, physiological, pharmacological and/or environmental countermeasures will help crew members reduce disturbances of circadian rhythmicity; sleep disturbances, or homeostatic sleep drive, thereby reducing the associated performance deficits?
- What technological and procedural advances can minimize the probability of error by astronauts whose abilities may be impaired by fatigue or circadian disruption? How can advances in computer-aided decision making, on-board training or smart check lists be

applied to offset cognitive deficits? How can physical ergonomic arrangements be used to mitigate the effect of fatigue in space operations?

- What are the long-term consequences of the use of countermeasures designed to mitigate performance decrements associated with sleep loss and/or circadian disturbances?
- How do countermeasures intended for other physiologic systems (e.g., exercise, activity schedules) interact with sleep, circadian organization, and waking function in long duration space flight? How might the timing of such countermeasure administration be used to improve sleep, circadian organization or waking performance?

3.5 Immunology, Infection and Hematology

Team Leader: William T. Shearer, M.D., Ph.D.
Baylor College of Medicine
(See Table 2)

It has long been known that space flight affects the body's fluids, including blood, in dramatic ways, and it has been suspected that space flight exerts possible harmful effects upon the body's immune system. As the flight duration increases, the risk that crew members will be exposed to infectious agents from other crew members and the spacecraft environment will also increase. Among the possible effects on the immunohematological system are an increase in the susceptibility to infectious diseases and carcinogenesis (see the Critical Path Roadmap, Section 3.1). The factors of space travel that might predispose humans to a secondary state of immunodeficiency disease include stressors, such as psychological and physical stress, isolation, microbial contamination, malnutrition and space radiation.

The current research program has involved the utilization of several Earth-based models, including the study of subjects exposed to the 9-month isolation and exposure of the Antarctic winter, those who are sleep-deprived for several days, and subjects who are enclosed in a self-containment capsule for 6 months. Also, animal research has focused on the antiorthostatic murine model and on isolated tissue and cellular studies. The specific measurements of human immune function and viral reactivation have included those of plasma and cellular cytokines, specific antibody formation, lymphocyte proliferation to recall antigens, and viral DNA quantitation in blood, oral secretions and urine. Animal studies have consisted of measuring several aspects of inflammation and cellular adherence, viral clearance mechanisms and immune responses. Data from these human and animal studies show that stressors (behavioral, environmental, physical and infectious) can modulate the immune response, reactivate latent viruses and enhance the pathogenesis of primary infections by microbial agents. In addition, the hormonal alterations that occur subsequent to an individual's perception of an environmental situation as a stressor interfere with normal pathophysiologic host defense mechanisms (e.g., acute inflammation).

The goals of this research area are to: determine whether immune function will be altered and infections or malignancies increased in astronauts in long-term space travel; determine whether genetic or functional microbial changes impact on the pathophysiology of infections, and develop countermeasures to alleviate the changes in immune and stem cell function, microbial infections and virus reactivations. Eight interrelated themes have been identified in this research area, including the emerging field of stem cell biology as a possible new model system with which to examine the effects of long-duration space travel:

- A. **Effects of long-duration space flight upon specific T-cell and B-cell mediated immune responses.** This theme addresses the possibility that secondary immunodeficiency would develop in astronauts on long voyages due to the side-effects of space travel, such as neuroendocrine axis-mediated stress, microbial contamination, malnutrition and solar radiation. Defects in primary and secondary antibody and T-cell responses may be produced by these factors. All of these side-effects are known to negatively influence specific immunity, but systematic studies of sufficient numbers of study subjects are needed to go beyond the experiences previously recorded as anecdotal evidence.
- B. **Alterations of cellular and humoral elements of innate immunity in long-duration space flight: cellular metabolism and adhesion molecule biochemistry.** Among the unknowns of space travel is the behavior of the cellular and humoral components of innate immune responses. The migration of leukocytes, cell surface expression and function of adhesion molecules, secretory and phagocytic pathways of neutrophils and monocytes/macrophages are all subjects that need investigation. In addition, an important aspect of innate immunity requiring study is the healing phase of the inflammatory process following infection or trauma.
- C. **Role of mucosal immunity in long-duration space flight.** The mucosal immune system has not been adequately studied in the context of the possible harmful effects of space travel. Using ground-based models of some effects of space flight, it will be possible to systematically examine the elements of mucosal immunity such as viral and bacterial clearance, antigen capture by phagocytes, and generation of neutralizing antibodies, cytotoxic T-cells and other T-cell effector functions.
- D. **Microbial infections in long-duration space flight.** A critical question to be addressed is whether the immunosuppressive effects of space travel will lead to acute microbial infection, chronic viral infection and development of malignancy. Based upon the models of primary immunodeficiency, transplantation and AIDS, it is to be expected that given enough space-related immunosuppression, viruses such as Epstein-Barr virus will be reactivated and may produce untoward consequences.
- E. **Effects of the space environment on microorganisms and their host interactions.** These would include the pathogenesis of opportunistic infections by bacteria, fungi and viruses. Little is known about the space environment's effects on microbial processes (e.g., secretion, adherence, virulence) and adaptation which may lead to increased pathogenesis. Even a normal immune system may not be able to cope with these space-adapted microbes.
- F. **Development of autoimmune disease in long-duration space travel.** As the consequences of disturbing the normal balance of immune system components may be the development of autoimmune responses and disease, it will be important to check for autoantibody production and immune complexes in humans exposed to space travel. Human and animal ground-based models of space flight may be utilized to evaluate this possibility.
- G. **Effects of long-duration space flight upon stem/progenitor cell biology and function.** This theme addresses the concern that long-term space travel will adversely affect stem cell biology and development. Stem cells play a critical role in the lifelong regeneration of many organs, including those of the hematopoietic, gastrointestinal, musculoskeletal and nervous systems. Long-term exposure to radiation, in particular, is a concern since the potential for mutagenesis and consequent failure of development or malignant transformation are real possibilities. In addition, it is also possible that known or unknown alterations of cytokine production, adhesion receptor display and signal transduction pathways induced by radiation, stress, infection and/or nutritional deprivation might adversely affect long-term stem cell functioning. Accordingly, these issues are also

worthy of investigation. Use of in vitro culture systems, animal transplantation models and molecular informatics are among the appropriate tools that may be used to address these critical questions.

- H. **Countermeasures.** This theme is concerned with the development of specific countermeasures for the possibilities of altered immune responses, viral reactivation and increased infections by other microbial agents in space flight and their consequences. These countermeasures may include immunotherapeutic, pharmacologic, behavioral, environmental, dietary, physiologic and adaptive approaches to prevent the possible harmful effects of long-term space travel upon human immunity and infection.

Research Questions

The following questions are provided to assist the applicant in developing a proposal that is focused on relevant research. They are not complete, and project proposals may address other questions fitting within the guidelines above.

Do factors associated with space flight (e.g., physical and psychological stress, environment, microgravity, nutritional status, radiation, confinement, sleep deprivation, fluid shifts) affect one or more of the following?

- ◆ humoral or cell mediated immune function
 - ◆ innate immune factors
 - ◆ mucosal immunity
 - ◆ tolerance or immune surveillance
 - ◆ reactivation of latent viruses
 - ◆ susceptibility to microbial infections
 - ◆ cancer risk
 - ◆ allergy and hypersensitivity
 - ◆ response to bacterial, viral or fungal agents; or to factors released from the agents (e.g., endotoxin)
 - ◆ stem cell/progenitor cell biology and function
 - ◆ wound healing
- Do alterations in these systems (areas) pose significant risks to crew members in a manner that exposes them to unacceptable medical risks?
 - Are there assays that reliably predict changes in these systems, and can these assays be adapted to space travel?
- What specific infectious agents will crew members be exposed to and what are their sources?
 - What diagnostic and environmental monitoring needs to be developed?
 - Do space flight conditions alter growth rates, mutation rates or pathogenicity of microorganisms?
 - Do space flight conditions affect reactivation and shedding of latent and persistent viruses?
 - Are there potential alterations in host – microbe balance (e.g., do microfloral agents change over time during space flight)?
 - Do unique environmental factors inside the spacecraft promote the transmission and activity of microbial pathogens or cause increased risk of infection, allergy or hypersensitivity reactions independent of altered immune function?
 - Can additional new ground-based models be developed to simulate stressors of space flight conditions?
 - Are there countermeasures that would prevent the specific changes associated with space flight (e.g., related to malnutrition, psychological stress, viral reactivation, microbial infections, immune alterations, autoimmunity, wound healing, stem cell function and development)?

3.6 Muscle Alterations and Atrophy

Team Leaders: Susan Hamilton, Ph.D.
and
Robert J. Schwartz, Ph.D.
Baylor College of Medicine
(See Table 2)

Exposure to reduced gravity during space travel profoundly reduces the loads placed on muscle. Astronauts lose muscle mass and strength while in space, and, therefore, their ability to function efficiently upon re-exposure to gravity is reduced. Reloading of muscle can also produce muscle injury. Individuals with weaker muscles are less likely to survive a life-threatening emergency requiring muscle strength. Similar wasting of muscles can arise on Earth with prolonged bed rest, limb immobilization, severe burns, malnutrition, nerve injury, motor neuron diseases, cancer, HIV infection and aging.

The research program of the Muscle Alterations and Atrophy Team is driven by the following critical risks identified through the Critical Path Roadmap (see Section 3.1):

- Loss of skeletal muscle mass, strength and/or endurance;
- Inability to adequately perform tasks due to alterations in motor performance, muscle endurance, and structural and functional properties of the musculoskeletal system;
- Propensity to develop skeletal muscle injury, connective tissue dysfunction and bone fractures due to debilitation or maladaptation of the neuromuscular system; and
- Potential impairment of other organ systems secondary to the changes in skeletal muscle.

The primary goals of the team are to develop countermeasures that reduce the above risks and to optimize diagnostics and therapeutic interventions to ensure crew safety, well-being, and performance in changing environments. Attaining these goals will allow humans to live and work in microgravity for extended duration and will minimize neuromuscular injury associated with readaptation to Earth's gravity. To accomplish these goals, the team will elucidate the basic mechanisms involved in microgravity-induced muscle atrophy and, simultaneously, develop countermeasures to regulate these changes.

The development of the most effective countermeasures requires delineation of the signal transduction pathways altered by removal of gravitational load. Most mechanistic insights about the probable causes of muscle atrophy during space flight will initially be obtained from animal and human ground-based models. Where appropriate and feasible, pre- and postflight, noninvasive methods may be applied to the study of these mechanisms in astronauts. Experiments performed in animals will provide guidelines for design of human experiments and will provide molecular/biochemical markers of muscle atrophy. Ground-based longitudinal experiments on human subjects will use several approaches (e.g., bed rest, immobilization, single limb unloading) to address related mechanistic questions. These human studies should facilitate the design of flight experiments by demonstrating ranges of individual characteristics and sensitivities to adaptive interventions and countermeasures, which will guide refinement of testable hypotheses.

Research Questions

The following interrelated questions are provided to assist the applicant in developing a proposal that is focused on the critical factors within the scope of this research area. As stated earlier, this

program will emphasize both applied and basic mechanistic approaches for the development of effective countermeasures. The questions are neither prioritized nor complete. Project proposals may address other questions fitting within the programmatic interests defined above.

- What signaling pathways are altered by load, and how do these pathways cross talk to direct an integrated response?
- What are the targets of the signaling pathways pertinent to the phenotypic response to altered functional demand?
- How are proteolytic pathways (e.g., calpains, caspases, ubiquitin-proteasome) involved in protein degradation processes altered in unloading-induced atrophy?
- Are pro-apoptotic pathways activated in altered loading conditions?
- How are the proliferative and differentiation processes of satellite cells affected by altered loading?
- What are the molecular mechanisms that regulate muscle fiber phenotype with altered load?
- What is the molecular mechanism by which skeletal muscle fibers adjust their length (sarcomere assembly and disassembly) in response to an altered functional working range of the muscle?
- What changes occur at the level of protein and gene expression in response to altered muscle loading and countermeasures?
- What are the mechanisms that regulate the changes in the structural, biochemical and functional properties of the neuromuscular tissue in response to altered load?
- What changes occur in muscle metabolism, composition and energetics in response to altered muscle loading and countermeasures?
- How do soluble factors, such as cytokines, growth factors and hormones contribute independently or synergistically to the response of muscle to altered loading?
- How do influences extrinsic to skeletal muscle systems (such as radiation, stress, and altered fluid and hemodynamic balance) influence the ability of muscle to function in and recover from altered load?
- How do fluid redistribution and altered circulation accompanying exposure to microgravity affect the metabolism, clearance and activity of muscle anabolic and catabolic agents?
- What are the effects of muscle responses to altered load on other body systems (e.g., endocrine, bone, cardiovascular, neurovestibular)?
- What structural, biochemical and functional changes in sensory or motor neurons result from, or act to modify, muscle responses to altered loading?
- By what mechanism does the physical inactivity of skeletal muscle produce a systemic metabolic dysfunction (e.g., metabolic/insulin resistance syndrome or syndrome X)?
- How are low- and high-intensity work-induced muscle fatigue altered in a real or simulated space flight environment (that includes unloading, radiation, temperature and other factors)? What are the mechanisms to explain these alterations?
- What are the mechanisms through which muscle injury, repair or regeneration occurs following alterations in loading? How can countermeasures positively influence these processes?
- What are the optimal countermeasures for maintenance of muscle and bone structure and function?
- What interventions can precondition and/or rehabilitate muscle to changes resulting from altered loading?
- How can concepts derived from animal models be confirmed in humans and applied to optimize human performance in space?
- How can ground-based models (e.g., human bed rest; limb unloading in humans and animal models) be used to evaluate and optimize countermeasures?

- Do hormonal, pharmacological, gene therapy and nutritional interventions used as countermeasures increase the efficacy of exercise protocols in maintaining muscle mass and function? To what extent?
- What nutritional interventions are needed to minimize losses in muscle mass, strength and endurance?
- How much individual variability is there in baseline values for any given muscle phenotype and in the response of that phenotype to the proposed countermeasure?
- To optimize selection of persons most resistant to the negative consequences of microgravity on muscle, what variables might be considered to pre-screen potential astronauts for long duration space flight?
- Can new countermeasures be found by developing and applying high throughput screens or other novel approaches that capitalize on advances in understanding the mechanisms underlying unloading atrophy or aberrant muscle repair?

3.7 Neurovestibular Adaptation

Team Leader: Charles M. Oman, Ph.D.
 Massachusetts Institute of Technology
 (See Table 2)

The neurovestibular problems associated with space flight (e.g., space motion sickness, disorientation, oculomotor deficits, postflight postural instability and gait ataxia) typically arise when astronauts transition from 1-G to 0-G, just when their physical and cognitive performance is critical for mission success and safety. Similar problems are expected on exploration-class missions when astronauts make the transition from 0-G to partial G, or from 0-G to an artificial gravity environment. During the shuttle era, space neurovestibular research focused on understanding the effects of unweighting of the otoliths on the vestibulo-ocular reflex (VOR) and on predicting space sickness susceptibility. NSBRI's current neurovestibular research program is investigating context specific pre-adaptation, preflight visual orientation and 3-D spatial memory training countermeasures and developing ways to improve our assessment of postflight posture, locomotion and gaze control problems. Future program expansion will include several new areas of emphasis, including artificial gravity, postflight neurovestibular rehabilitation, improved anti-motion sickness drugs and other areas defined below.

The neurovestibular adaptation research program is aimed at developing scientifically-based countermeasures against the vestibular problems associated with space flight and addresses five major space neurovestibular risk areas identified through the Critical Path Roadmap (see Section 3.1):

- **Disorientation and reduced performance on cognitive and physical tasks**, including vehicle egress, especially during/after G-level changes (associated with acute-spontaneous and head-movement-contingent vertigo, nystagmus, oscillopsia, saccadic errors, reduced dynamic visual acuity).
- **Impaired neuromuscular coordination and/or strength** (gait ataxia, postural instability).
- **Impaired cognitive and/or physical performance** due to spatial disorientation, motion sickness symptoms or treatments (including short term memory loss, reaction time changes, drowsiness, fatigue, torpor, irritability, ketosis) as a result of changes in g-level, or use of artificial gravity.
- **Autonomic dysfunction** (including cardiovascular, respiratory, gastrointestinal, sleep and mood changes) which may be of vestibular origin.

- **Permanent impairment of orientation or balance function** due to microgravity or radiation (causing chronic imbalance, gait ataxia, vertigo, chronic vestibular insufficiency, poor dynamic visual acuity).

The goals of the program are to develop countermeasures that ultimately will allow crewmembers to: avoid disorientation, meet the physical requirements of emergencies, treat motion sickness without side effects and safely control vehicles and systems. Nine interrelated countermeasures-oriented themes define the scope of this research area:

- Adaptive generalization and context-specific adaptation;
- Artificial gravity;
- Visual (multisensory) orientation, navigation and spatial memory;
- Drug countermeasures;
- Postflight locomotion and gaze assessment;
- Neurovestibular rehabilitation;
- Vestibular effects on autonomic function;
- Effects of weightlessness, stress, isolation, immobilization and diet on vestibular function; and
- Potential mechanisms for and diagnosis of irreversible neurovestibular changes.

As stated earlier, NSBRI research is ultimately directed at the development of countermeasures. Basic research projects must plausibly lead in that direction. If specific countermeasures are proposed, they will ultimately have to be proven safe and practical, and their potential impact on other physiological systems must be understood. In addition, the dependent measures used to assess countermeasure effectiveness must be defined. Individual differences in susceptibility to neurovestibular problems must be recognized. Currently, research is being conducted at the cognitive, behavioral, system, organ and cellular level, using quantitative techniques in both humans and animals. Molecular methods may also be appropriate. Much of the research is interdisciplinary and involves collaborations between investigators at multiple institutions. Use of mathematical models as a research tool is encouraged. (N. B., The current NASA postflight neurovestibular assessment is a 15-minute exam of neurological symptoms and signs, dizziness, motor performance and gait.)

Research Questions

The following questions are provided to assist the applicant in developing a proposal that is focused on relevant research. The questions are listed under the nine themes. They are not complete, and many questions are relevant to more than one theme. Project proposals may address other questions fitting within the programmatic interests defined above.

Adaptive Generalization and Context-Specific Adaptation

- Can we enhance an individual's ability to adapt to multiple environments through adaptive generalization? What are the sensory-motor responses that must change in a functionally adaptive manner during prolonged space flight? Does such adaptation does take place? How can it be reliably measured? Can these adaptive responses be trained to be context-specific?
- What is the evidence for and the physiological bases of oscillopsia, disorientation, ataxia and reduced dynamic visual acuity reported by crewmembers, particularly while making head movements during re-entry and immediately postflight?
- To what extent can gravireceptor-dependent motor responses be pre-adapted in context-specific ways, so astronauts can rapidly transition between 1-G and 0-G, 0-G and partial G, or 0-G and artificial G with minimal performance impairment or motion sickness? How long does the pre-adaptation last? Must the context cue be associated with active movement?

- How do countermeasures (e.g., artificial gravity, inflight exercise or preflight training) affect adaptation rates and levels? How do rates and levels associated with physiological (sensorimotor, autonomic, emetic) adaptation to microgravity and 3/8 G on Mars correlate with operational performance changes?
- What are the appropriate space flight analog environments that can be used as test beds for evaluating neurological adaptation, adverse operational implications, countermeasures and impacts of adaptation on other anatomical and physiological systems?

Artificial Gravity

- What are the pros and cons of artificial gravity (AG) as a countermeasure against the effects of 0-G on neurovestibular function and on cognitive and physical performance? What are the advantages and disadvantages of large radius continuous AG vs. short radius intermittent AG, and how are these influenced by mission duration and post-landing environment (Mars vs. Earth)?
- Can humans successfully adapt to working perpendicular to the angular velocity vector?
- How can transitions be eased?
- What is the maximum tolerable rotation rate for a given G level? What is the best habituation schedule?
- What is the relationship between psychosocial factors and vestibular adaptation to altered gravity?

Visual (Multisensory) Orientation, Navigation and Spatial Memory

- How do visual and nonvisual cues interact to influence human orientation perception and perceptual motor behavior? Does 1-G training in simulated “agravic” real or virtual environments improve 3-D spatial memory and performance in orientation and navigation tasks?
- How do visual, vestibular and haptic cues contribute to inversion illusions, visual reorientation illusions, extravehicular-activity acrophobia, disorientation and poor 3-D spatial memory in 0-G?
- What is the physiological basis of inversion illusions, visual reorientation illusions, EVA acrophobia, disorientation and 3-D spatial memory problems in 0-G?
- How is the human sense of place and direction neurally coded in 0-G?
- Can preflight training techniques (e.g., virtual reality simulations) be used to alleviate these problems and to evaluate emergency procedures?
- How can 0-G immersive teleoperation displays be designed to reduce disorientation and/or motion sickness?

Drug Countermeasures

- Can improved anti-motion sickness drugs, delivery systems and dose and side effect monitoring systems be developed? Drugs must be effective, easily and safely used over days to weeks with minimal side effects and must not impair adaptation. Ground-based experimental models for evaluating 0-G pharmacokinetics and for assessing the effectiveness of drug countermeasures are needed.

Postflight Locomotion and Gaze Assessment

- What causes the profound impairments of posture, gaze and locomotion stability in many returning astronauts (and in vestibular patients), and how can these be quantified?
- What causes the large differences in level of impairment observed among different people? How do these differences correlate with physiological and operational performance changes?

- How are the multiple, mutually dependent sensorimotor systems responsible for locomotion altered by exposure to space flight? For example, what is the role of the vestibulo-ocular, vestibulo-collic and vestibulo-spinal reflexes in 3-D control of locomotion?
- How are target acquisition, smooth pursuit and saccadic mechanisms programmed during locomotion? How do oculomotor and gait control systems interact during locomotion and head turning? How is this interplay affected by space flight?
- Can long-term exposure to space flight impair sensorimotor plasticity?
- What roles do visual cues play in postflight locomotor control?
- In an altered sensory environment, does motor control require increased cognitive resources? Does this multi-tasking impair performance? Can a dual-task paradigm be used to monitor adaptation?
- What is the linkage between space flight-induced changes in sensory-motor control and astronaut functional performance?
- What measures represent composite and global indicators of locomotor and/or gaze dysfunction after space flight? What measures are the most efficient and sensitive indicators of changes in locomotion and/or gaze? What is their correlation with functional performance after space flight.

Neurovestibular Rehabilitation

- Can preflight or inflight training, sensory aids, prostheses and assessment techniques improve inflight orientation and gaze control? Can they improve postlanding functional task performance and also postural and locomotor control?
- How can somatosensory information be used to assist adaptation?
- What are the relative contributions of neurovestibular adaptation, neuromuscular deconditioning and orthostatic intolerance to postflight neuromuscular coordination, ataxia and locomotion difficulties?
- How does attention to a new sensory-motor task affect performance of a secondary task?

Vestibular Effects on Autonomic Function

- What is the physiological basis of space motion sickness? How does chronic space motion sickness (including space motion sickness) affect mood, initiative and interpersonal relationships?
- Does the neurovestibular response to weightlessness impair postlanding cardiovascular regulation and contribute to orthostatic intolerance? In what effective frequency range? Can an effective countermeasure (e.g., AG) be developed to exploit this knowledge?

Effects of Weightlessness, Stress, Isolation, Immobilization and Diet on Vestibular Function

- How can changes in vestibular function due to weightlessness be distinguished from the normal responses to stress, isolation, diet and normal background physiological variability? What countermeasures can be developed?

Potential Mechanisms For and Diagnosis of Irreversible Neurovestibular Changes

- How might very long duration exposure to 0-G or partial G cause irreversible (pathophysiological) changes in central or peripheral vestibular function or development, or cause acceleration of the normal aging process? Would some individuals be more susceptible than others? What is the potential time course? How could such changes be reliably detected at an early stage?
- How does serum calcium homeostasis impact otoconial turnover?

3.8 Radiation Effects

Team Leader: John F. Dicello, Ph.D.
Johns Hopkins University School of Medicine
(See Table 2)

Exposure to higher than normal radiation levels is one of the major health risks to humans on long-term space flights (see the Critical Path Roadmap, Section 3.1). This exposure results primarily from galactic cosmic rays (GCR) and solar particle events. The protons and high Z, energetic particles (HZE) involved may exert sizable biological effects even at low fluence, and there are considerable uncertainties associated with secondary particle effects (e.g., HZE fragments, neutrons, etc.). Although the health risks from exposure to radiation (x rays, gamma rays, or electrons) encountered on Earth are comparatively well known, the health risks from space radiation are not well known. Several independent causes contribute to the overall risk to astronauts exposed to the complex space environment on exploration-class space missions. Of primary concern is the induction of cancer. However, central nervous system damage is also a potentially mission-compromising event because of the possibility of cell loss from radiation damage affecting central nervous system functional integrity. Recent studies also point to previously unknown mechanisms of radiation-induced cellular pathologies based on the communication between damaged and undamaged cells and the induction of unstable states that lead to late expression of genetic damage. Space radiation appears to be uniquely effective in causing such cellular changes.

The current NSBRI radiation research program is highly focused on one model system: the mammary tumor system in the female Sprague-Dawley rat. The biological endpoint being addressed is cancer. Institute resources for this research area are not likely to be sufficient in the near term to cover the full range of risk-related radiation research but must be used to address only topics of the highest priority, where substantive results and accomplishments can be expected in a single-award time frame. Therefore, research applications should propose projects with direct applicability to one or both of the following problems:

- Improving the predictions of risks to human health from space radiations, and/or
- Providing effective countermeasures that will significantly reduce these risks.

Each application must provide a strategy and schedule that would describe how the results of the proposed experiments would finally yield data that could be used directly for providing a quantitative estimate of risk or for producing an effective countermeasure. It is important that this strategy be as explicit as possible and contain a schedule that would yield results within the necessary time frame.

The countermeasures referenced here are biological or biochemical agents useful for modulation of significant radiation effects, which offer substantial promise as prevention or intervention tools in managing of human risk arising from space-radiation exposures. Proposed agents shall have demonstrated efficacy for chemoprevention of malignancies with low or no significant toxicity. Radiation countermeasure agents shall be based on scientific understanding of their likely efficacy against protons and high-energy, highly charged nuclei (HZE particles).

Research in this area will focus on five interrelated themes:

- Development of countermeasures for mitigating the effects of radiation exposure;
- Development of markers for determining risks and monitoring the efficacy of countermeasures;
- Determination of carcinogenic and CNS effects of space radiation;

- Determination of acute and long-term pathological responses of rapidly renewing organ systems at risk; and
- Characterization of differences in cell and molecular mechanisms for pathological effects for high- versus low-linear energy transfer (LET) radiation in defined model systems.

Research Questions

The following questions are provided to assist the applicant in developing a proposal that is focused on relevant research. They are not complete, and project proposals may address other questions fitting within the programmatic interests defined above.

- What is the probability of cancer induction and/or CNS damage by protons and HZE's in animals?
- Are there complementary *in vitro* cellular and subcellular experiments that can be done to establish the mechanisms of carcinogenesis *in vivo*?
- Are there chemical or biological agents that can be implemented to mitigate radiation risks?
- Are there radioprotectants that mitigate acute exposures?
- Are there classes of minimally toxic agents that will globally reduce radiation risks?
- Are organ-specific countermeasures useful for reducing radiation risks on long-term space missions?
- What is the methodology to extrapolate the biological results to human risk?
- How can existing epidemiological data for humans be utilized to interpret biological data in terms of risk assessments for exposures in space?
- What are methodologies to extrapolate biological results to low-dose risk predictions?
- Are there effects or mechanisms associated with high-LET interactions which are not produced in low-LET interactions?
- Are the risks from the various radiations in space independent?
- Are there environmental stressors that exacerbate the disease risks?
- Do changes in radiation quality as a function of spacecraft material and thickness significantly alter risk?
- Are the biologic effects at low doses resulting from primary, incident protons sufficiently similar to photons that the photon data can be used for proton exposures?
- What is the dependence of biological response on fluence and fluence rate?
- Are the single-particle events from the HZE's in space properly simulated with present accelerator-based exposures?
- What non-radiation factors contribute to the observed radiation responses?
- Are there significant risks from radiations in space other than those associated with carcinogenesis and CNS damage?
- Are there short-term or intermediate-term biomarkers that can be used to monitor biological consequences of radiation exposure with adequate sensitivity and lack of confounding factors?
- Are there nutritional supplements that will provide radiation protection and/or boost organ function and/or environmental factors that can significantly alter radiation risks in space?

3.9 Technology Development

Team Leader: Vincent L. Pisacane, Ph.D.
Johns Hopkins University Applied Physics Laboratory
(See Table 2)

The goal of this research area is to develop technologies that will lead to a better understanding of the barriers to long-duration space exploration and to assist in the development of countermeasures to assure safe and productive missions. Primary attention will be directed toward technologies that support the ground-based and space flight research of the other eleven NSBRI research areas. Seven of these areas are described in this announcement and four are described in a previous announcement (Announcement NSBRI 99-02, December 28, 1999). Such research may include studies involving either human or animal subjects, or both. The Technology Development Team will create systems and tools such as sensors, instrumentation, devices and intelligent software and systems that support the NSBRI research teams and the space life sciences research community at large. The tools developed will be used for studies including human and animal subjects, to develop countermeasures and to support remote medical care. The specific objectives of the technology development program are to develop sensors, devices, instrumentation and systems that: support the investigation of the effects of space flight on human physiology and behavior; apply this information toward developing the techniques and technologies that will sustain humans during future missions through the development of countermeasures; and benefit the quality of life and medical care on Earth. Specific technologies of interest include those that:

- Identify the risks of space flight to humans,
- Identify the impediments to effective work and operation on and near other celestial bodies,
- Assess the physiological and psychological status of test subjects,
- Determine a proposed countermeasure's effectiveness,
- Monitor a countermeasure's effectiveness during space flight,
- Support remote health maintenance and medical care, and
- Exploit these advances to improve the quality of life on Earth.

A subsidiary interest is to promote technology transfer by collaborating with industry early in the development process, especially utilizing the NSBRI's Industry Forum, so that the products can be made available to support other research activities that can benefit society.

The Technology Development Team will generally focus on projects that will deliver a specific product in a specified period of time, typically one to three years. Proposals will be expected to be of a maturity equivalent to that of a typical NASA Phase A (Conceptual Design) study.

The following eight interrelated themes will be used to build a focused technology development program:

- A. Monitoring/Sensing Systems.** Systems are needed for monitoring humans and animals in both Earth- and space-based research protocols. A broad range of measures, including physiology, performance and environment, are needed along with methods for telemetering and storing the information.
- B. Sample Collection & Processing.** Success of many research protocols is predicated on the collection, handling and processing of biological specimens. New and unique methods are required to collect samples, with minimal impact on the subject, and to reliably process the samples in near real-time.

- C. **Analysis/Decision Support Systems.** Large amounts of biochemical, histology, assay, image and signal information need to be presented and analyzed in support of the research efforts. Advanced, automated and quantitative tools are needed to support the growing analysis and decision-support requirements.
- D. **Human-Machine Interfaces.** There is a growing need to integrate machines with human subjects and researchers. It is necessary to expand interfaces to all senses for monitoring and stimulation. Virtual reality displays and enhanced control modalities should be adapted for simulation and tactical use.
- E. **Informatics.** It is necessary to analytically predict physical, chemical and biological system responses. The use of modeling and simulation methods can be made practical if advanced tools and techniques are developed. Integrated and searchable data archives are also necessary.
- F. **Interventional Modalities.** Therapeutic and pharmacologic methods hold promise as countermeasures for microgravity effects and as treatment for other medical conditions. Development of advanced interventional resources is necessary.
- G. **Cell-Based Tools.** Experiments that require the processing of cells are manually intensive and time consuming. Automated ground-based tools and space-based methods that do not rely on gravity need to be developed.
- H. **Cost-/Time-Saving Devices/Methods.** There is an overarching need to identify and implement devices and methods that will facilitate lower-cost research that can reliably be completed in less time.

Research Topics

The following topics are provided to illustrate the research scope of this area. They are not complete; project proposals may address these and other topics singly or in combination.

Advanced Non-/Minimally-Invasive Physiologic Monitoring. There is a critical need to develop or adapt existing monitoring systems that can be used in human and animal research. These monitoring systems should be non- or minimally-invasive and miniature, relative to the experimental subject, and capable of remote data transmission for both ground-based and inflight environments. Monitoring parameters of interest include vital signs, core body temperature, eye motion, body fluid chemistry and hormone, endocrine and melatonin levels.

Non-Invasive Monitoring of Soft Tissue Composition and Bone Material Characteristics. Technology is desired that would be used to monitor muscle atrophy during long-term space flight. Compact, easy-to-use methods accessible to important sites in the trunk and lower extremity are preferred. Technology is also needed to monitor the possible effects of space flight or disuse on the material properties of bone, independent of anisotropy, and must be able to structural or density effects. Methods must account for bone anisotropy and must be able to measure properties in principle loading directions in accessible lower-extremity sites.

Remote Spatial Position Measuring System. A spatial positioning system which provides accurate six degree of freedom information of human body segments is required. The device should be small, portable and light weight with low/no susceptibility to spacecraft electromagnetic interference (EMI) and magnetic field influences.

Minimal-Size Animal Data Measurement and Telemetry System. Tethered measurement systems inhibit or alter responses in small animals. Tethering humans greatly limits their ability to do the kind of work they need to do during space flight missions. The measurement of parameters

from unencumbered subjects is required. The measurement system should be extremely small, have a range of >10 feet and handle multiple channels with high resolution, large dynamic range and moderate bandwidth.

Pathogen Monitoring. The need exists to be able to detect and identify pathogens, including bacteria, fungi and viruses, in air, water samples, food and human specimens. Emphasis should be given to analysis of small sample volumes, fast read-out and automated methods.

***In Vivo* Mechano-Transduction Monitoring.** New techniques to elucidate basic mechanisms of muscle and bone atrophy and mechano-signal transduction are needed. Possible approaches include mechanically-stimulated altered fluorescence, altered gene expression and proteomics.

Novel Sample Processing Strategies. New automated delivery devices are needed to increase throughput of cell culture and small animal models in ground-based radiation experiments. An automated computer-driven image analysis system is needed for histological tissue sample analysis.

Optimized Blood/Fluid Sampling. Frequent measurement of analytes in blood or other serous fluids can indicate the need for or effectiveness of countermeasures. Ideally, a non-invasive, body-worn device that can continuously collect and analyze tiny quantities of blood or serous fluid would be the result. Current technical constraints, however, provide only intermittent samples that may need to be analyzed by a separate instrument. The immediate need is to provide an easy-to-use, non- or minimally-intrusive method of withdrawing or collecting such fluids without the problems and discomfort of frequent blood draws.

Automated Sample Handling. Biochemical assays of cellular function require multiple steps, in which cells of interest are isolated from other cells, incubated with replacement media, exposed to particular reagents and then analyzed. The techniques for these steps in sample handling intermediate between obtaining cell samples and final biochemical analysis cannot be readily performed in microgravity. There is a need for a generic means of handling samples, perhaps using solid supports, by which sequential incubations and washes of cells might be performed.

Improved Assay Techniques. There is a need to analyze samples immediately in space flight, in order to study cell surfaces and contents (flow cytometry, surface plasmon resonance), protein contents (proteomics), gene expression (gene chips), solute composition (capillary electrophoresis, mass spectroscopy), gas composition (mass spectroscopy), etc. It is essential that equipment (not limited to the examples above) be developed for these analyses. This equipment must be small in size and mass, suitable for space flight, and either fully-automated or simple to operate by minimally trained personnel.

Advanced Gait Perturbation Device. A device to generate a small perturbation to gait during free walking is required to analyze the detrimental effects of exposure to microgravity on the balance system of astronauts. The device will be used for ground-based studies and should apply consistent perturbations across multiple trials.

Enhanced Virtual Reality Environmental System. A virtual reality (VR) system could provide stimulation to correct neurovestibular problems, enhance psychological well being and monitor performance/alertness. The deliverable system's overall properties must yield technology that is minimally obtrusive and unencumbering, such as head-mounted displays, include multiple sensory systems and significantly extend the current state-of-the-art VR systems.

Human Biochemistry Simulator. It has been determined that many aspects of human biochemistry change during space flight. Computer models and simulations of human biochemistry (both on Earth and in microgravity) need to be developed and validated. The biochemistry simulator would be utilized as both a predictive and diagnostic instrument. The system would be portable, self-contained, have low mass and would be used in both ground-based and space-based experiments.

Minimally-Invasive Therapy. Because medical care in a space flight environment must be performed with limited resources, technology is needed to treat critical conditions such as blunt trauma and internal bleeding. In addition, for extended-flight scenarios, minimally invasive surgical techniques that could prevent the evolution of a critical condition and restore minimal function are desired. These systems should be portable, versatile and suitable to be performed with limited expertise in an adverse environment.

4.0 APPLICATION PROCEDURES

4.1 General Instructions

Applications are to be submitted on the grant application form PHS 398 (rev. 4/98). These forms are available electronically from grants.nih.gov/grants/funding/phs398/phs398.html. If you do not have access to the Internet, you may order the forms by calling GRANTSINFO at (301) 435-0714 or sending an e-mail to grantsinfo@nih.gov. Instructions for completing the application are found in the PHS 398 application form.

DO NOT SUBMIT THIS APPLICATION TO THE NIH. INSTEAD, FOLLOW THE SUBMISSION INSTRUCTIONS BELOW. Please direct any questions that you may have concerning this application form to the NSBRI: telephone – 713-798-7412, fax – 713-798-7413.

Submit the signed, original application and twenty-five exact photocopies and twenty-five collated sets of appendix materials, in one package, to:

NATIONAL SPACE BIOMEDICAL RESEARCH INSTITUTE
REF: NSBRI 00-01
ONE BAYLOR PLAZA, NA-425
HOUSTON, TX 77030-3498.

Applications must be received before 5:00 p.m. CDT, Friday, June 16, 2000. FAXED proposals are not acceptable, neither are electronic mail (e-mail) responses.

4.2 Special Instructions

Research Area – Each application must address one, and only one, of the eight research areas discussed in Section 3 of this announcement. Applications that impact more than one area should be directed to only one primary research area although a secondary research area may be identified on the application. Submitters are requested to identify the primary and, if appropriate, the secondary, research area in the title blank of Section 2 of the face page of the application form (*Response to Specific Request for Applications or Program Announcement*). The “Yes” and “No” boxes may be left blank.

Potential applicants may contact the Team Leaders identified in Table 2 to assist them in determining which research area is most appropriate to apply to or to discuss the timeliness or relevance of their planned research to the research areas described in this announcement. In addition, ALL countermeasure-related proposals should contain a special statement specifying the countermeasure readiness level of the proposed project (see Section 3.1 and Table 1).

Letter of Intent – To facilitate planning for the review process, investigators are requested to advise the NSBRI of plans to submit a proposal responding to this announcement by sending a non-binding letter of intent to propose by April 14, 2000 to:

NATIONAL SPACE BIOMEDICAL RESEARCH INSTITUTE
REF: NSBRI 00-01 – Letter of Intent
ONE BAYLOR PLAZA, NA-425
HOUSTON, TX 77030-3498.

This letter should be limited to two pages or less and should contain the names and institutional addresses of all investigators and co-investigators involved in the project, a descriptive title and the primary research area for which the proposal will be intended.

Duration of Proposed Research – Proposals for ground research may be submitted for a maximum duration of three years funding, with an assumed starting date of October 1, 2000. Space flight investigations should be proposed for a nominal duration of three years funding, with an assumed start date of April 1, 2001. As stated below, flight investigations will be selected in October 2000 for a brief definition period. Following this definition period, proposals may be declined or selected for funding and assigned to a mission. Although some flight investigations may take longer than three years to complete, investigators are requested to assume their flight studies will be completed by October 2004.

Total Annual Cost – It is expected that the average annual total (direct + indirect) cost of selected proposals will be between \$200,000 and \$250,000. In general, the annual total cost of a single proposal may not exceed \$400,000.

Inclusion of Women and Minorities in Research Involving Human Subjects – The NSBRI has adopted the NIH Policy regarding this matter. Thus, women and members of minority groups and their subpopulations must be included in NSBRI-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.

Human Subjects and Vertebrate Animals – For proposals involving human subjects or vertebrate animals, please follow the instructions for grant application form PHS 398 (rev. 4/98). If IRB or IACUC review is pending at the time of submission, follow-up certification of IRB or IACUC approval from an official signing for the applicant organization must be sent to the National Space Biomedical Research Institute at the address listed for proposal submission. The NSBRI will forward this information to the scientific review panel administrator. For a list of information to be included in the follow-up certification, please refer back to the form PHS 398 (rev. 4/98) instruction booklet.

Space Flight Investigations – Proposals for space flight experiments should be submitted separately from ground-based research proposals and not combined in one package. It should be assumed that flight investigations proposed in response to this announcement will be completed by October 2004, with the space flight resources available between October 2001 and October 2004. Investigators should note that flight resources on the Space Shuttle for the next few years and during the early phase of the International Space Station are expected to be minimal, and the competition for those resources will be intense. Thus, flight proposals should represent mature studies and be based on compelling evidence from previous flight studies or appropriate ground-based research. Flight experiments normally require limited baseline or control studies on the ground, and these should be included as part of a flight experiment proposal. It should be noted that pre- and postflight studies on crewmembers, even with no inflight data collection or protocol activity, are considered flight experiments and should be proposed as such. Preparatory ground research designed to define a flight experiment should be proposed as a ground-based study.

Investigators interested in proposing flight experiments should refer to the *Space Life Sciences Flight Experiments Information Package, 1999*, issued by the International Space Life Sciences Working Group. This package is available on the World Wide Web at peer1.idi.usra.edu/peer_review/nra/99_HEDS_03.html.

Section 5.0 of that document concerning international application forms and instructions for proposal preparation should **not** be followed; form PHS 398 should be used instead.

Special Ground Facilities – A variety of special ground research facilities, including centrifuge facilities, bed-rest facilities, etc., are available for use by investigators submitting proposals in response to this announcement. Interested investigators are referred to the *Space Life Sciences Ground Facilities Information Package, 1999*, also issued by the International Space Life Sciences Working Group and available on the World Wide Web at the same site peer1.idi.usra.edu/peer_review/nra/99_HEDS_03.html.

The NSBRI will negotiate appropriate use of those facilities on behalf of selected investigators, but investigators must include the cost of using these facilities in their proposal.

Special Travel and Reporting Requirements – Principal investigators selected in response to this announcement will be expected to attend two, two-day research team meetings each year at a location to be determined and one annual three- to four-day general investigator workshop/retreat in the Houston, Texas area. Budgets should reflect the costs associated with these meetings and should include a statement indicating that this travel is a special requirement. Selected investigators will become part of the NSBRI's intramural research program and will be expected to provide an annual progress report. Progress is reviewed by the NSBRI's Board of Scientific Counselors. In addition, investigators will be required to provide annual project information for inclusion in NASA's *Life Sciences Program Tasks and Bibliography*.

Data Management Plan – Most data collected through NSBRI support are required to be placed in a central Institute data archive. Investigators should plan for delivering their data to the NSBRI archive and must include the cost of data archiving in their submitted proposal. If selected, a data management plan, including a list of the data products and a schedule for their delivery, must be prepared and submitted to the NSBRI. No additional costs should accompany this plan.

5.0 COMPETITIVE PROCESS

5.1 Review and Selection Process

Applications will be evaluated for scientific and technical merit and for the likelihood that the research proposed will have a significant impact on achieving the goals stated in this announcement. The initial review will be carried out by an appropriate panel of experts convened under the auspices of NSBRI's independent Board of Scientific Counselors. As part of the initial review, all applications will receive a written critique and be discussed by the panel. Only those applications deemed to have high scientific merit will be assigned a numerical score. Applicants will receive a copy of the panel's comments and score as soon as they are available. Those proposals deemed to be in the competitive range for this submission will receive a second-level review by the NSBRI scientific program directors to determine relevancy of the proposed project to the research program in the particular research area under consideration. Applicants should be aware that some meritorious proposals may not be selected for funding. Selection recommendations are prepared by NSBRI management, reviewed by the NSBRI External Advisory Council and approved by the

NSBRI Board of Directors. (N.B. The initial review group will also examine the provisions for the protection of human and animal subjects and the safety of the research environment.)

Flight proposals may be selected for a brief definition period during which it will be determined whether or not it is feasible to actually carry out the proposed investigation in space within a reasonable time and what the realistic costs of the proposed study are. Flight proposals may be declined following this definition period.

5.2 Evaluation and Award Criteria

The following criteria will be used in the evaluation:

Significance: Is the proposal responsive to the needs of the NSBRI, as expressed in this announcement? 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? What is the likelihood that the proposed research will lead to new countermeasures or tests of the utility of countermeasures?

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? Are there strong interdisciplinary components?

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? Are novel experimental approaches considered? Do preliminary results support the new approaches?

Investigator: Are the scientists in the project, including collaborators, suitably trained for the proposed work? Is the work proposed appropriate to the experience level of the principal investigator and other researchers (if any)?

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

Selection will be based on the merit score awarded by the peer review panel, on the programmatic relevance as determined by NSBRI management, on cost, and, in the case of flight proposals, on the feasibility of actual implementation. For studies involving human subjects, the adequacy of plans to include both genders and minorities and their subgroups as appropriate for the research goals and the plans for subject recruitment and retention will be taken into account.

6.0 SCHEDULE

The following schedule is planned for the formation of new research teams by the National Space Biomedical Research Institute:

Letter of Intent Due:	April 14, 2000
Proposal Due:	June 16, 2000
Selection Announcement:	August 2000
Funding Initiation:	October 2000

Original signed by

Laurence R. Young, Sc.D.
Director
NSBRI

Original signed by

Ronald J. White, Ph.D.
Associate Director
NSBRI

Original signed by

Bobby R. Alford, M.D.
Chairman of the Board and CEO
NSBRI

February 22, 2000

Date