

NATIONAL SPACE BIOMEDICAL RESEARCH INSTITUTE

Research Announcement

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

Formation of New Research Teams

December 28, 1999

NSBRI 99-02

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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 four *new* research areas:

- neurobehavioral and psychosocial factors;
- nutrition, physical fitness and rehabilitation;
- smart medical systems; and
- integrated human function.

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 four areas. Only investigators interested in becoming members of these four teams should apply to this announcement. Another research announcement recruiting investigators to participate in the eight current NSBRI research areas is expected to be released in February 2000.

Each of the four new 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 provisional Team Leaders selected for the organizational phase of the new teams are listed in Section 3 (Table 2).

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. Thus, 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 initial competitive process used by NASA to select the NSBRI, most of the Institute's research program currently 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 the postflight impairment of the cardiovascular response to orthostatic and exercise stress;
- *Human Performance* – 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). This present announcement (Announcement NSBRI 99-02) is to form four new research teams. The third announcement, scheduled for release in February 2000, will 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 four 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 long-term human space flight, the NSBRI focuses its research program on the needs of exploration-class space missions. These missions (e.g., missions to Mars) pose the greatest challenge to future space travelers, and meeting their challenge with appropriate countermeasures lies at the core of the NSBRI's responsibility. A typical Mars-type mission might involve trips of six months to one year each way, with a stay on Mars of one to two years. Effective 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.

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 web site (<http://criticalpath.jsc.nasa.gov/>) starting in early 2000. 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 Neurobehavioral and Psychosocial Factors

Provisional Team Leader: Nora D. Volkow, M.D.
Brookhaven National Laboratory
(See Table 2)

Astronauts aboard extended-duration missions will endure isolation and confinement in the harsh space environment to a much greater degree than has been experienced previously. Maintaining individual neurobehavioral functioning and group psychosocial effectiveness will be vital to assuring mission success. The Neurobehavioral and Psychosocial Factors Team is focused on research that will ensure that astronaut neurobehavioral health is maintained during prolonged missions, that astronaut performance capability is facilitated by appropriate habitat and human-systems interfaces, and that crew functioning is effectively optimized.

The scope of this research area includes: (1) Identification of the neurobehavioral and psychosocial risks to crew health, safety, well being, performance and productivity during long-duration space missions; (2) Evaluation of the effects of space-related stressors (i.e., habitability constraints, microgravity, radiation, work requirements, sleep deprivation, perceived risks, restricted communication with Earth and boredom) on physiological and psychological functions of individuals and crews; (3) Development of accurate, practical techniques and approaches to monitor behavior and performance capability during missions; (4) Development and validation of countermeasures to manage or mitigate space-related risks to neurobehavioral functions and to enhance health, motivation, safety and performance during such missions; (5) Identification of strategies to maintain motivation and ensure an effective quality of life in space; and (6) Development of procedures to determine optimal leadership style, crew composition, organization and communication with Earth.

Table 1. COUNTERMEASURE READINESS LEVELS

BASIC RESEARCH	1. PHENOMENON OBSERVED AND REPORTED, PROBLEM DEFINED.
RESEARCH TO PROVE FEASIBILITY	2. HYPOTHESIS FORMED, PRELIMINARY STUDIES TO DEFINE PARAMETERS, DEMONSTRATE FEASIBILITY.
COUNTERMEASURE DEVELOPMENT	3. VALIDATED HYPOTHESIS, UNDERSTANDING OF SCIENTIFIC PROCESSES UNDERLYING PROBLEM.
COUNTERMEASURE DEMONSTRATION	4. FORMULATION OF COUNTERMEASURES CONCEPT, BASED ON UNDERSTANDING OF PHENOMENON.
COUNTERMEASURE OPERATIONS	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.
	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.
	9. COUNTERMEASURE FULLY FLIGHT TESTED AND READY FOR OPERATIONAL IMPLEMENTATION.

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

A. Biological mechanisms of neurobehavioral dysfunction. Addresses adverse neurobehavioral events associated with alterations of nervous system function due to prolonged exposure to conditions encountered during long-duration space missions (microgravity or altered gravity, radiation, loss of geophysical cues, isolation, restricted motility, confinement, boredom and stress). The focus is on the nervous system response at the cellular, molecular or organismic level to conditions likely to be encountered during these missions.

B. Motivation, cognition and performance. Concerns the assessment and enhancement of individual information processing, cognitive functioning, motivation and operational performance during space missions.

C. Individual factors. Addresses the individual factors involved in astronaut selection, training and performance, the individual issues related to crew monitoring and psychological support during and rehabilitation following a mission, and the impact of individual factors on strategies to deal with potential psychiatric problems and neurobehavioral dysfunction during a mission.

D. Pharmacology in space. Addresses issues related to the utilization and efficacy of psychoactive and psychotherapeutic agents during space missions, including research into pharmacokinetics and drug bioavailability, changes in the blood-brain barrier, drug interactions, psychological and behavioral side effects of medications and their therapeutic effectiveness.

E. Team and interpersonal optimization. Focuses on issues related to leadership, crew selection and composition for individual space missions, crew functioning during such missions (e.g., training, social interaction, time factors, decision making and error management) and crew-ground interactions. In particular, the study of communication is of particular importance as multinational cooperation assumes a more prominent role in mission design and operation.

F. Organizational, cultural and management factors. Examines the effects of cultures (organizational, professional and national) and management goals, policies and priorities on crew communication, performance, problem solving and, ultimately, health and safety.

Research Questions

The preceding themes are associated with a broad range of research questions that currently exceed NSBRI resources for this area. Therefore, this initial announcement focuses on the following specific research questions related to themes A through D. Many of the research questions related to themes E and F will be covered in future initiatives. For convenience, research questions related to themes A through D have been organized below within four categories: risk assessment, mechanisms and processes, countermeasures, and medical diagnosis and treatment. Many questions cut across the research themes and these categories. Individual project proposals should address the relevant research questions below.

Risk Assessment

- What are the fundamental behavioral and social stressors during long-duration missions that will most likely affect crew performance, both individual and team?
- What model(s) of psychological adaptation in isolated and confined environments will best predict the effect on individual and team performance over the course of the mission?
- What inter-subject and intra-subject factors predict vulnerability to performance failure during prolonged space flight? What factors predict psychological dysfunction for long-term space missions? How can a measurement system be applied to individuals with different primary languages and cultures?
- What noninvasive measures and techniques can be developed to assess the neurobehavioral, neurobiological, neuroendocrine and/or neuroimmune consequences of stress in individuals?

What biological, psychological and social factors can be identified that enable a prediction of individual vulnerability to stress effects?

- What model(s) of behavioral health and task performance best predict and provide guidelines for effective treatment of illness during space flight (e.g., depression, anxiety, trauma and other neuropsychiatric dysfunctions)?
- What are the most common and the most serious neurobehavioral and psychosocial threats (perceived and real) posed to individual astronauts on long missions, and what countermeasures effectively mitigate these threats?
- What techniques and technologies can be developed to objectively evaluate human performance? What are the most effective means to monitor the psychological and neurobehavioral health and well being of astronauts, given that such monitoring should conserve critical resources such as crew time and spacecraft demands (e.g., power usage)? What tools can be developed to monitor astronaut cognitive performance during a mission (i.e., basic information processing such as working memory, focal attention, ability to retrieve information from long-term memory)? What tools can be developed to detect cognitive performance deficits during a mission?
- How can a measurement system provide a means of interpreting the performance information in a manner that indicates the likelihood that an astronaut can successfully perform a specific task? How can a measurement system be used to track and advise regarding the use of countermeasures to enhance performance?

Mechanisms and Processes

- What are the acute and long-term effects of exposure to the space environment on human cognition and performance capabilities, including processes of sensation and perception, mood, learning, vigilance, cognition, problem-solving, decision making and motor skills?
- What are the acute and long-term effects of exposure to the space environment (microgravity, confinement, stress) on the nervous system (at the cellular, molecular or organismic levels) and on related neurobehavioral mechanisms, including neurobiology related to behavior and mood regulation?
- What are the effects of space-related stressors (i.e., radiation, microgravity, work schedules, chronic sleep deprivation, perception of risk, constrained space and motion, continuous noise, boredom/monotony/routine) on central nervous system anatomy, neurochemistry, regulatory behaviors (e.g., appetite, sleep), physiology, neuroendocrinology and neuroimmune interactions, including the effects of simultaneous exposure to multiple stressors as would occur in space?
- What are the effects of space-related stressors on the neurobehavioral functions underlying performance capability, mood and group cohesion?
- What are the acute and long-term effects of exposure to the space environment on human emotion and psychological responses, including emotional reactivity, stress responses, long term modulation of mood and vulnerability to affective disorders?
- What are the impacts of long-duration space flight and microgravity on the pharmacokinetics and pharmacodynamics of drugs intended as countermeasures for the neurobehavioral effects of space flight?
- How do human-machine interactions change over the course of a long-duration mission?
- What are the organizational requirements for support of human performance and the development and maintenance of an optimal behavioral ecosystem in space, including the level of crew autonomy and the distribution of authority, task scheduling, resource allocation and distribution, and implementation of behavioral countermeasures?
- What are the acute and long-term effects of exposure to the space environment in gene expression in animal models?

Countermeasures

- What countermeasures can be developed to minimize impairment of performance or reduced morale by space-flight-related stressors? What combination of behavioral and physiological countermeasures will optimally mitigate specific performance problems associated with stress during a prolonged mission?
- What pharmacological approaches are effective in improving performance in long-duration space flight? How long do these effects last? What are the secondary effects of countermeasure pharmacology (e.g., hypnotics and anti-nauseants) on performance?
- What countermeasures can be developed to optimize motivation and improve the quality of an astronaut's life during extended space missions?
- What are the best countermeasures for rapidly recognizing and rapidly managing neurobehavioral dysfunction, emotional and stress-related dysfunction, neuropsychiatric dysfunction and social-psychological dysfunction?
- What countermeasures can help crewmembers deal with stressors upon return from space? How can families best re-integrate astronauts after long missions? What are the long-term sequelae of life-changes and other aspects of long-duration space missions?
- What pharmacological approaches can be developed to minimize damage from potential neurotoxic effects of radiation?

Medical Diagnosis and Treatment

- What techniques and methods can be developed for use in flight to effectively monitor and detect neurocognitive difficulties during a prolonged mission?
- What techniques and methods can be developed for use in flight to effectively monitor and detect emotional distress and other forms of neuropsychiatric function during a prolonged mission?
- What training is required by the crew or ground personnel in order to recognize psychological difficulties experienced by crewmembers? What role can telemedicine effectively play in the detection and management of such difficulties?
- What drug delivery systems for neurobehavioral problems are best suited to space missions?

3.3 Nutrition, Physical Fitness and Rehabilitation

Provisional Team Leader: William J. Evans, Ph.D.
University of Arkansas for Medical Sciences
(See Table 2)

This research area focuses on nutrition, physical fitness and rehabilitation, and the interactions among them. Research in this area should utilize an integrative approach to develop broad-based, practical countermeasures appropriate for exploration-class missions. These countermeasures, based primarily on human responses to nutrition and exercise and on sound rehabilitation principles, should focus on removing, or reducing to appropriate levels, deficiencies in human functional ability during space and planetary exploration. Thus, they should prevent the

Table 2. Provisional Team Leaders for the New NSBRI Research Areas

Neurobehavioral and Psychosocial Factors

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progression of functional impairments beyond an acceptable level and enable rehabilitation to a functional status appropriate to the specific challenges of the mission phases as they occur.

For the present announcement, the scope of this research area is limited to proposals that address one or more of the following issues: development of countermeasures with the characteristics discussed above; development of performance-based methods to quantitatively assess countermeasure effectiveness; and evaluation of the effectiveness of existing or new ground-based human models of space flight for simulating integrated, multidisciplinary events.

The following interrelated research topics characterize the scope of this research area:

- **Nutrition.** Addresses: (1) development of mission-phase-dependent nutrient requirements; (2) design of countermeasures to avoid single or multiple, concurrent nutrient deficiencies; (3) nutritional/endocrine interactions and influences on metabolic integrity; and (4) development of approaches to assess nutritional status that relate to functional outcome.
- **Exercise/Physical Fitness.** Addresses: (1) quantification of baseline physiological and physical functions necessary for individuals to perform multiple space operational tasks (e.g., EVA, emergency egress, piloting skills, etc.) involving one or more muscle groups (arms, legs, hands, whole body); (2) quantitative assessment of muscle strength and fatigability of specific muscle groups, maximal oxygen uptake and autonomic vasomotor functions before, during and after space flight; (3) identification of combined dietary and exercise prescriptions to assure physical fitness of individuals for an exploration-class mission; and (4) identification of the physical fitness requirements for operational tasks that may change throughout the duration of the mission, especially following transitions between different gravitational environments.
- **Rehabilitation.** Addresses: (1) identification of the tasks necessary to an exploration-class mission; (2) evaluation of those physical tasks identified for such a mission; (3) study of rehabilitation modalities and interventions necessary to maintain performance in the identified tasks during and following gravitational changes; and (4) determination of how physical modalities (e.g., ultrasound, laser, etc.) used in rehabilitation may be adapted to the space environment for the treatment of injuries.

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.

- What characterizes the astronaut's physiological adaptations during the different exploration-mission phases, and what are the predictors of metabolic imbalance, musculoskeletal deterioration and sensorimotor dysfunction during such a mission? What is the interdependence of motor performance and exercise capacity on nutritional and hormonal factors?
- What are the most appropriate astronaut studies relevant to this research area that can and should be carried out prior to the introduction of full laboratory capability on the International Space Station?

- What are the interactions among nutrition, combinations of different exercise modes (e.g., resistance and/or aerobic exercise), and the stressful environmental factors (e.g., sleep deprivation, circadian disturbances, intense work schedules) associated with long-term space flight?
- Why does food intake typically decrease during space flight? Research should address the potential impact of appetite control, social/behavioral influences, gastrointestinal function, physical activity and alterations in sleep/circadian cycles.
- What are the multiple systems effects of individual countermeasures that seem to ameliorate some of the adverse physiological effects of space flight? For example, can a resistance exercise training regimen designed to minimize muscle and bone loss during space flight favorably impact cardiovascular mechanisms associated with orthostatic tolerance?
- How much of what kind of periodic exercise pattern, dietary change or rehabilitation strategy is required to maintain and restore normal motor function? Research should take into account the mission-phase changes that occur in the threshold and sensitivity of neural, muscular, cardiovascular and metabolic systems to perturbations that occur during exercise.
- What is the relationship between nutritional requirements and different types of exercises or other countermeasures likely to be used during space flight, given the changes in nutrient intake that may occur during flight? This research may focus on nutritional requirements to maintain nitrogen or calcium balance or to ameliorate losses. For example, research could focus on calcium and protein needs and/or dietary supplements and hormonal interventions. The use of dietary supplements and any drug therapy should also include a strategy to evaluate safety, pharmacokinetics and effectiveness.
- What is the impact of restricted caloric intake on countermeasure effectiveness? (Reduction in caloric intake is routinely reported during space missions and may be secondary to neuro-vestibular problems and motion sickness.)
- What is the role for nutraceuticals, such as enriched foods and physiologic regulators, in the management of metabolic imbalances?
- How should nutritional and physical status be determined during space flight, including measurement of body mass, determination of surrogate metabolic markers, and development of biosensors and monitoring strategies to enable remote evaluation?
- Do the interactions of muscle-strengthening exercises with other systems, such as cardiovascular and neurovestibular systems, depend more on flight phase or individual adaptability? Can exercises intended to enhance musculoskeletal function also have a beneficial effect on visual-vestibular coordination and on locomotion?
- What are the contributions of reduced gravity, restricted food intake, reduced exercise levels, confinement and isolation on acquiring and maintaining motor skills and performance?
- What is the minimal level or threshold of exercise (intensity, duration and frequency) necessary to maintain or to restore specific functional capability during space flight?
- What countermeasures involving diet, exercise and rehabilitation should be used to maintain health and adequate performance of astronauts during and after an exploration-class mission?

(It is likely to be unrealistic to attempt to maintain preflight physical fitness and metabolic function throughout the course of prolonged space flight, and that, in fact, this may be contraindicated if certain physiological adaptations to space flight are beneficial to the space traveler.)

3.4 Smart Medical Systems

Provisional Team Leader: Jeffrey P. Sutton, M.D., Ph.D.
Harvard Medical School
(See Table 2)

This research area focuses on health maintenance and acute and chronic medical care during exploration-class missions. It includes the development of new and advanced concepts of medical monitoring, diagnostic and therapeutic systems. Such systems could assist in training, decision making and therapeutic intervention. The ultimate goal of this research is to develop a smart, integrated medical system that would assist in the delivery of quality health care on an exploration-class mission. This area includes the following topics:

- New or novel medical and surgical techniques;
- Novel sensor development;
- Advanced drug synthesis and delivery systems;
- Robotic medical assistance systems;
- Automated medical data systems, including reliable patient data acquisition and analysis with minimal crew oversight; and
- Automated decision support, training and diagnostic – therapeutic systems.

The following five interrelated themes characterize the research in this area:

- **Patient monitoring and data management.** Concerns the development of methods and systems for minimally invasive and non-invasive individual patient monitoring and data capture, data communication, display and storage. This activity should be tightly coupled with the development of individualized patient models.
- **Diagnosis.** Addresses the topic of assisted diagnosis and includes the development of methods to provide reliable diagnoses of events during each phase of an exploration-class mission.
- **Treatment.** Focuses on development of novel approaches to treat acute and chronic medical and dental conditions, taking into account the constraints of exploration-class missions.
- **Medical system integration.** Addresses the development of an adaptable, easy to use, unobtrusive, and safe medical and decision support system with intelligent components that will include reliable patient monitoring.
- **Autonomous medical operations.** Concerns the development of: autonomous agents that serve as teacher, diagnostician and guide for medical and surgical therapy; systems and devices appropriate for ongoing medical training and augmentation of both knowledge and skill; and onsite manufacturing ability, allowing medical instruments, pharmaceuticals and biomaterials to be fashioned from primary materials.

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.

Novel sensor systems for monitoring and diagnosis. Sensors for medical use on exploration missions should have low noise/high specificity, low power requirements and minimal use of consumables. They should be modular, evolvable, adaptable, unobtrusive, comfortable, safe and easy to use. Non-invasive or minimally-invasive systems are of special interest, as are sensors that capture data relevant to a broad range of clinical and environmental parameters. Examples may include micro-array sensors for various metabolites, tools for assessing genomic and proteomic expression, and novel means of tissue monitoring (e.g., optical imaging).

Novel three-dimensional imaging strategies. New devices and approaches are needed to provide improved anatomical and functional definition both in routine monitoring and in acute, critical diagnostic circumstances. Three-dimensional data collected inflight should be readily comparable with ground-based data acquired prior to flight. Research is needed to develop automatic measurement capabilities that routinely pass the data on to physiological modeling and decision support components of the medical care system.

Decision support systems and knowledge bases for diagnosis and treatment. Medical care in a remote, isolated environment will depend on automated and semi-automated processes, alerts and reminders, and methods for aiding human decision makers. This, in turn, requires the ready availability of medical knowledge resources, including textbooks, atlases, guidelines, formularies, diagnostic decision aids and other tools. Methods for organizing and retrieving knowledge relevant to a medical problem, inferring conclusions, developing and customizing diagnostic and treatment plans, and monitoring responses are needed.

Novel therapeutic modalities. Recognizing that facilities and specialty expertise for treating illness and injury will be limited, research is needed to identify alternative approaches that emphasize less invasive therapeutic interventions. Methods and devices that can be used by individuals with limited expertise under adverse space-flight conditions are required. The focus should be on approaches that minimize resource requirements and restore functionality, allowing mission completion.

Remote fabrication and pharmacological production for space. Highly flexible ways to produce biological and non-biological materials, tools and medications will be needed to supply exploration-class missions with additional or unplanned equipment, drugs and prostheses, as they are required.

Intelligent general-purpose reasoner. A valuable computer-based reasoning system (reasoner) would assist in the planning of optimal diagnostic and therapeutic courses of action, predict likely outcomes, and design realistic simulations and training scenarios individualized to a specific person. The reasoner would use comprehensive models to help integrate data, compute diagnostic consequences of the data, and provide real-time inference for emergency interventions and mentoring.

Decision support system for monitoring. Formalized approaches are needed to decide how changes in measured data should be brought to the attention of crew and/or ground support personnel. These approaches require domain-specific models of both short- and long-term

changes in physiological status and status of the crew's environment and life-support systems. Computational techniques are required to direct monitoring systems, allocate monitoring resources across systems, and determine when, to whom and how urgently to report monitoring results. Communication latencies, dropouts and limited bandwidth introduce unavoidable disturbances. System architectures and collaborative approaches therefore need to be developed to support the requirement for shared decision making and data management.

Human-computer interaction techniques. New techniques are required to facilitate monitoring, alerting, mentoring and training. To make the content and procedures of a sophisticated health support system available to crewmembers, the system must be easy to use and employ innovative representations of the data and information. Research is needed to define and refine virtual reality visualization, including innovative user interface technologies for feedback and control.

Intelligent systems for mentoring and training. Supervision of crew-conducted procedures by automated processes can make them safer and more effective. For example, an intelligent mentor system, in the form of personalized avatars for each astronaut, could use personalized models of a patient to guide surgical procedures and prevent errors. Similar capabilities could create personalized training scenarios that would allow a crewmember to practice emergency procedures and plan treatments or surgical procedures. Such a mentor would help prevent errors by providing guidance and feedback from the mentoring system.

3.5 Integrated Human Function

Provisional Team Leaders: James B. Bassingthwaighe, M.D., Ph.D.
and
Martin J. Kushmerick, M.D., Ph.D.
University of Washington
(See Table 2)

This research area seeks to develop a sufficient understanding of human function (from molecules to systems) to enable a reliable evaluation and prediction of an astronaut's safety and functional capacity. The critical path analysis mentioned in Section 3.1 identifies the biomedical risks of long-duration missions, and much of the NSBRI's research effort is aimed at studying the major physiological systems involved in those risks. The Integrated Human Function research area is responsible for supplying the holistic, integrated knowledge necessary for understanding the human as a total organism. This understanding of human function needs to be quantitative and predictive and must be sufficient to enable simulation and planning for adequate and timely responses to challenges *en route* and for successful accomplishment of tasks at destination and return to Earth. It will serve as an integrated repository of knowledge on mechanisms and their coordinated operation in the intact human and as a means for evaluating efficacy of proposed countermeasures.

Realization of this level of understanding will enable medical planning and therapy when needed and analyses of human responses to altered physiology in ground-based research, flight preparations during the mission and rehabilitation on return. Research in this area requires the development of strategies for and implementation of mechanism-based computational models and simulations of human functions. Such software modules should be extensible, reusable, interoperable and retargetable, and they need to be based on cellular, tissue- and organ-level mechanisms. It

should be possible to leverage and exploit existing standards, methods and WEB-supported models and databases such as the High Level Architecture (HLA) for simulations of the Department of Defense, the Common Object Request Broker Architecture (CORBA), the designs incorporated in the Physiome Project and the NLM Visible Human, and the Department of Energy's nascent program on the Virtual Human whose perspective is similar to that of NSBRI but whose targets differ. The goal of this research area is to address the relevant multi-system problems in an integrated manner in space explorations and provide appropriate spin-offs for terrestrial problems. A personalized human model will eventually be developed for use in the Smart Medical Systems described in Section 3.4. Comprehensive individual models of the anatomy, physiology, functional status, medical and environmental history of each astronaut will play a significant role in monitoring, diagnosis, treatment and outcomes prediction, and will allow for training and simulation during long-term missions. This is not an exercise in descriptive mathematics and programming.

Proposals targeted for this research area must demonstrate an integrated computer-based approach to scientific knowledge and information about human function with the underlying cellular, tissue- and organ-level mechanisms. Ultimately this research will produce a "digital human." Such a digital human will be dynamic, quantitative, predictive and integrative. It will be robust in the sense that the generic model will be "tunable" for individual astronauts and useful for analyses of animal experiments. It will synthesize mechanistic information vertically and horizontally, including knowledge from the other NSBRI research teams: digital cells + digital organs + digital systems = digital human. Research may contain hypothesis- or discovery-driven experimental work and computer-based modeling as well as systems for computation and database documentation, but the laboratory elements and computer systems must be fully justified and integrated in the project. Developing a meaningful digital human is clearly a multi-year project, and this research announcement only begins this task. Therefore, applicants might propose an analysis of one or more component cells and organs that are understood well enough to demonstrate clearly the feasibility of the project and outline the path for measuring progress and a plan for extending that analysis into a fully-integrated human system.

Because of the importance of changes to selected systems in the microgravity environment, the focus of proposed projects should be one or more of the following physiological systems: cardiovascular, bone, muscle and sensory-motor systems. One middle-to-long-range goal of this program is the development of a functional model of the human musculoskeletal system. This functional model would be based on an anatomical model such as the Visible Human, with a complete set of bones, soft tissues and muscles defined as to their internal structure, function, regulation and metabolism. This musculoskeletal model will eventually be used to deal with problems related to locomotion, responses to exercise and disuse, metabolism and energetics in the intact human. Other goals of the program are to develop generic models of skeletal and cardiac muscle, eventually suitable for understanding and interpreting data on the short- and long-range effects of exercise, microgravity, prolonged lack of usage, injury, dietary deficiency, etc. These models would be composed of a set of submodels encompassing the features of mitochondrial metabolism, myofibrillar protein mass and behavior, cellular energetics, substrate usage and regulation, signaling pathways, control of gene expression especially regarding the processes of atrophy and hypertrophy, and endocrine and neural signaling. More near-term metabolic and endocrine models might be focused on the musculoskeletal and cardiovascular systems. An example would be the influences of dietary content (e.g., of fat) on muscle atrophy and hypertrophy, on insulin sensitivity, on the relative usage of carbohydrate, fat and protein metabolism, on the effects of exercise and disuse on insulin-sensitive receptor proteins, growth hormone, GLUT4, and on the transport capacity of sarcolemma for glucose. In the atrophying heart, there are addi-

tional risks of arrhythmia with changes in the ionic, metabolic, pH and calcium balances. Whole-cell and whole-heart modeling are encouraged in the interests of describing and predicting responses to stress, diet, injury and atrophy, both in microgravity and upon reentry into Earth's or Mars' gravitational fields.

The research may be organized to address and integrate certain fundamental physicochemical and biological processes, including:

- Signals and signaling pathways - biochemical, endocrine and electrical;
- Biomechanics and movement;
- Energetics, metabolism and their control mechanisms;
- Mass and energy transport and conservation with fluid, electrolyte and acid-base balances;
- Homeostatic regulation and multilevel control in hierarchical systems; and
- Adaptation and repair mechanisms.

These themes provide a solid basis for horizontal integration across cells, organs and systems. In addition, or alternatively, vertical systems integration (synthesizing molecular, biochemical, cellular and organ subsystems) may be chosen to address how hierarchical organization is achieved mechanistically. Finally, functional organization may be considered, such as:

- Multisystem models;
- Integrated sensorimotor models of performance;
- Tissue repair and long-term function alterations and rehabilitation; and
- Body distribution of exogenous therapeutic agents and endogenous signaling molecules and metabolites.

Research Questions

The first set below consists of generic questions. Following this set, as an example only, are more specific questions focused on the musculoskeletal system. The listed order of the questions does not imply a preconceived level of importance.

General System Questions

- What are the common mechanisms through which altered environments (e.g., microgravity, artificial atmospheres, radiation) change the functioning of multiple cells and organs? What mechanisms are specific, rather than common?
- What are the information and signals passed among cells and systems that result in a systemic response to the environmental alterations in the human response towards maintenance of homeostasis?
- There are many time courses of cellular- and organ-level responses (second to days) to stimuli. What approaches account for short time-constant and long time-constant mechanisms? How would these be integrated to produce oscillatory, stationary and steady-states appropriate for a wide range of physiological times?
- What are the normal physiological operational parameters of the component systems in the organism, the operating points in altered environments, and the magnitude of the functional reserve?
- How does one assess the response of an astronaut to altered environments using models of physiological mechanisms? How can this information be used to assess the efficacy of countermeasures?

- How can the analytical system and modeling approach chosen for your project be translated and transposed to other subsystems and thence to the intact human?
- What criteria and content is needed for a database of the required physiological information? Is it useful to extrapolate from current genomic and proteomic strategies, or are new strategies needed?

Specific Integrated Questions for Muscle and Bone

One way to begin the global task of a whole-body musculoskeletal model of muscles, tendons, ligaments, blood vessels, bones and joints is an analysis of the lower limb, which fatigues easily and atrophies in microgravity.

- What are the forces exerted by muscles on bone in terrestrial activities, and how do these change during activities at near-zero gravity, 0.16 G (Moon) and at 0.37 G (Mars)? How does the energy cost for contractile activity and substrate metabolism change as a function of gravitational load?
- What is the contribution to stored elastic energy in specific muscles and tendons in normal mechanics, and how does this change during adaptation to microgravity? How does one assess changes in the properties of these tissues in musculoskeletal function?
- What changes in gene expression and protein lifetimes govern the loss of mass of bone, heart and skeletal muscle during microgravity? Are these changes with atrophy related to changes in metabolic and energetic fluxes? Do these mechanisms account for the altered performance noted in human bed-rest models and/or in animal hindlimb suspension experiments?
- What are the relationships between force-generating mechanisms in skeletal muscle and changes in the structure and function of ligaments, tendons and bones?
- What is the role that the magnitude and patterns of mechanical stresses play in normal bone and muscle metabolism, on proprioceptive and other sensory signals, and on motor output? How are these effects and mechanisms altered in microgravity?
- Can the proposed analyses and models account mechanistically for the adaptations described from current astronaut flight information or from models of microgravity such as human bed-rest and animal hindlimb suspension?
- Does the analysis and model proposed suggest better or alternative experimental models for human and animal studies than those currently used?
- Can the analysis and model proposed be used to find surrogate measures that correlate with fundamental mechanisms derived from human or animal studies which would be useful for developing and testing countermeasures in human subjects?

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 99-02
ONE BAYLOR PLAZA, NA-425
HOUSTON, TX 77030-3498.

Applications must be received before 5:00 p.m. CDT, Friday, May 5, 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 four new 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 provisional 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.

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 March 17, 2000 to:

NATIONAL SPACE BIOMEDICAL RESEARCH INSTITUTE
REF: NSBRI 99-02 – 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:	March 17, 2000
Proposal Due:	May 5, 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

December 28, 1999

Date