NSBRI Nutrition, Physical Fitness and Rehabilitation Team Strategic Plan

10.0 NUTRITION, PHYSICAL FITNESS & REHABILITATION

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10.1 INTRODUCTION

Optimal human performance during space exploration requires the maintenance of all physiological systems, such as cardiovascular capacity, bone mineral density, and skeletal muscle function. Adequate nutrition and physical fitness affect all physiological functions and are dependent in part on each other. Not only must energy expended on physical activity be balanced by appropriate food intake, but also the timing of exercise with respect to food ingestion must be well planned since it impacts such important physiological effects as uptake of amino acids into muscle. Thus specific nutrients, ingested at the appropriate time, may help to maintain muscle mass. In addition, the appropriate combination of foods may result in release of glucose into the blood over time, and contribute to the maintenance of a high-energy status, which maximizes physical performance. The critical issues for nutrition are: (1) counteracting the observed anorexia of space flight; (2) determining nutrient needs to meet modified requirements due to space flight stressors including microgravity; and (3) developing new strategies including use of functional foods, supplements, and timing of food intake relative to specific activities that will optimize human performance. Equally important is remaining physically fit. Critical issues for physical fitness include: (1) development of appropriate protocols with respect to frequency, duration and intensity of aerobic and resistive exercise; (2) development of appropriate equipment (relevant to space flight) to maintain aerobic capacity and muscle performance (as measured by strength and endurance); and (3) optimizing the appropriate timing of exercise programs with respect to food intake and other activities (e.g. extra vehicular activity; EVA). Since physical activity will, in part, determine nutrient needs, and the optimization of nutrient delivery will in part depend upon blood flow and muscle mass (which are affected by physical activity), these two disciplines need to be considered together.

10.2 RISKS

Relevant risks (numbered in parentheses) that may be ameliorated by nutrition and physical activity interventions are found in many Discipline Areas of the Critical Path Roadmap:

<u>Food and Nutrition:</u>

- Inadequate Nutrition (Malnutrition) (7)
- Human Performance Failure Due to Nutritional Deficiencies (55)
- Difficulty of Rehabilitation Following Landing Due to Nutritional Deficiencies (54)

Muscle Alterations and Atrophy:

- Loss of Skeletal Muscle Mass, Strength, and/or Endurance (28)
- Inability to Perform Tasks Due to Motor Performance, Muscle Endurance, and Disruption in Structural and Functional Properties of Soft and Hard Connective Tissues of the Axial Skeleton (29)
- Inability to Sustain Muscle Performance Levels to Meet Demands of Performing Activities of Varying Intensities (30)
- Propensity to Develop Muscle Injury, Connective Tissue Dysfunction, and Bone Fracture Due to Deficiencies in Motor Skill, Muscle Strength and Muscular Fatigue (31)
- Impact of Deficits in Skeletal Muscle Structure and Function on other Systems (32)

Bone Loss:

- Acceleration of Osteoporosis (9)
- Fracture/Impaired Fracture Healing (10)
- Injury to Soft Connective Tissue (11)
- Renal Stone Formation (12)

Cardiovascular Alterations:

- Occurrence of Cardiac Dysrhythmias (13)
- Impaired Response to Orthostatic Stress (14)
- Diminished Cardiac Function (15)
- Manifestation of Previously Asymptomatic Cardiovascular Disease (16)
- Impaired Cardiovascular Response to Exercise Stress (17)

Human Behavior and Performance:

- Human Performance Failure Because of Poor Psychosocial Adaptation (18)
- Human Performance Failure Because of Sleep and Circadian Problems (19)
- Human Performance Failure Because of Neurobehavioral Dysfunction (21)

Immunology, Infection and Hematology:

- Immunodeficiency/Infections (22)
- Altered Wound Healing (25)
- Altered Host-Microbial Interactions (26)
- Allergies and Hypersensitivity Reactions (27)

Neurovestibular Adaptation:

- Disorientation and Inability to Perform Landing, Egress, or Other Physical Tasks Especially During/After G-Level Changes (33)
- Impaired Neuromuscular Coordination and/or Strength (34)
- Impaired Cognitive and/or Physical Performance Due to Motion Sickness Symptoms or Treatments, Especially During/After G-Level Changes (35)

Radiation Effects:

- Carcinogenesis Caused by Radiation (38)

Clinical Capabilities:

- Altered Pharmacodynamics and Adverse Drug Reactions (45)
- Development and Treatment of Space-Related Decompression Sickness (47)
- Difficulty of Rehabilitation Following Landing (48)

Multisystem Alterations:

- Post-landing Alterations in Various Systems Resulting in Severe Performance Decrements and Injuries (49)

The number of risks impacted by the level of nutrition and physical fitness is enormous, revealing the very interdisciplinary nature of the concerns of the Nutrition and Physical Fitness Team. In order to allow for the creation of a well-managed research program, we have modified the risks into broader "categories" of risk that can then be addressed more readily in our program. They are as follows:

- Suboptimal Nutritional Status due in part to Microgravity and other Stressors
- Suboptimal Level of Physical Fitness Induced by Microgravity and other Stressors
- Diminution of Skeletal Muscle Function
- Reduced Cardiovascular Capacity
- Radiation Enhanced Development of Cancer
- Decreased Cognitive Function
- Alterations in Sleep Patterns
- Poor Psychosocial Adaptation
- Depressed Immune Function
- Loss of Bone Mineral Density

10.2 GOALS

The Nutrition, Physical Fitness and Rehabilitation Team has the following goals for its program.

Risk-Based Goals

Goal 1: *Reduce Risk of Suboptimal Nutritional Status*

Goal 2: *Reduce Risk of Suboptimal Physical Fitness*

Goal 3: *Reduce Risk of Diminution of Skeletal Muscle Function*

Goal 4: *Reduce Risk of Reduced Cardiovascular Capacity*

Goal 5: *Reduce Risk of Radiation Enhanced Development of Cancer*

Goal 6: *Reduce Risk of Decreased Cognitive Function*

Goal 7: *Reduce Risk of Alterations in Sleep Patterns*

Goal 8: *Reduce Risk of Poor Psychosocial Adaptation*

Goal 9: *Reduce Risk of Depressed Immune Function*

Goal 10: *Reduce Risk of Loss of Bone Mineral Density*

Non Risk-Based Goals

Goal 11: *Develop Monitoring methods for assessment of food intake and physical activity.*

Goal 12: *Develop noninvasive techniques for assessing the effectiveness of diet and physical fitness interventions.*

Goal 13: *Develop Earth-based Applications for diet and physical fitness interventions*

Goal 14: *Integrate Research and Analysis*

10.4 DESCRIPTION AND EVALUATION OF CURRENT PROGRAM

The Nutrition and Physical Fitness team will develop countermeasures to most but not all of the risks noted in Section 9.2 above. Our primary immediate area of focus is on goals 1-5 and 11-13. Goal 1 (Reduce Risk of Suboptimal Nutritional Status) and Goal 2 (Reduce Risk of Suboptimal Physical Fitness) are our two primary goals. In fact, these two goals underlie all of the others, since if an individual is not physically fit and nutritionally replete, every organ system will be affected. The third goal (Reduce Risk of Diminution of Skeletal Muscle Function) is the focus of four of the five current research projects and has served to integrate nutrition and physical fitness in our current team program. Goal Four (Reduce Risk of Reduced Cardiovascular Capacity) follows from Goal 2, since optimal physical fitness will, by definition, improve cardiovascular capacity. Goal 5 (Reduce Risk of Radiation Enhanced Development of Cancer) is also addressed by the current research program with the Lupton radiation and colon cancer model. Additional non risk-based goals include developing monitoring systems for food intake and exercise which are noninvasive and require as little crew input as possible (Goal 11) and developing noninvasive techniques for assessing the effectiveness of diet and physical fitness interventions (Goal 12). Finally, nutrition and physical fitness countermeasures lend themselves very well to the development of Earth-based applications (Goal 13). For example, a well-designed amino acid supplement could improve protein synthesis not only in space but also on Earth and may be effective for patients with muscle loss due to stress, wasting, burns, etc. As another example, a resistance exercise device that effectively helps maintain muscle mass can also be used for individuals in nursing homes, under bed rest conditions, etc.

Although the potential impact of diet and exercise on reducing the risk of decreased cognitive function (Goal 6); alterations in sleep patterns (Goal 7); and the risk of poor psychosocial adaptation (Goal 8) is very strong, the basic science of how diet and exercise impact these risks is not as fully developed as it is for the other goals. For that reason we will concentrate our initial efforts in those areas where we expect to see the most immediate use of countermeasures based on strong basic science. Similarly, Goal 9 (reduce risk of depressed immune function) and Goal 10 (reduce risk of loss of bone mineral density) will not be a major component of the Nutrition and Physical Fitness Team's research agenda until the team becomes more mature. The specific risks of space flight to immune function are just now being elucidated. When the risks are more clearly defined, the diet and exercise countermeasures will be able to be developed in a more targeted manner. With respect to bone mineral density, NSBRI has a strong bone team, which has a variety of countermeasure approaches to this problem. In addition, NASA has a strong nutrition team with solid expertise in calcium metabolism and bone turnover. For these reasons we have chosen, at this time, to measure indicators of immune function and bone health in projects as appropriate, to cooperate/collaborate with NASA scientists in these areas, but not to have them as primary areas of focus in this initial period.

The Nutrition and Physical Fitness Team is new, and became operational in 2001. It presently consists of three nutrition countermeasure projects (Lupton, Wolfe, and Tobin), an "in flight" physical fitness project (Schneider) which is at the feasibility stage, and a modeling project (Cabrera) which was recently assigned to the team from the former Human Integrated Function Team. Table 10.1, entitled "Current Project Research Activities," summarizes for each current Nutrition and Physical Fitness Team project what risks are addressed, the experimental system, the countermeasure target and whether a project is part of the strategic steps of Phase 1, 2 or 3 Activities.

Specifically, *Nutritional Countermeasures to Radiation Exposure*, JR Lupton, PI, Texas A&M University, is testing the hypothesis that a particular diet intervention (an n-3 lipid and fermentable fiber combination) in rats should protect against radiation-enhanced colon cancer by targeting DNA damaged cells for apoptotic removal. It is directed to Goal 5: Reduce Risk of Radiation Enhanced Development of Cancer and will also contribute to Goal 1. Rats receive one of four diets, are exposed to heavy iron radiation at Brookhaven National Laboratory and are injected (or not) with a colon specific carcinogen. A variety of measurements are taken at three stages of the tumorigenic process (initiation, promotion, and final tumor development). This project also has a noninvasive component of monitoring changes in gene expression over time as a result of radiation and carcinogen exposure using microarray technology. If validated in rats, the diets and techniques can be modified for future studies in humans. This noninvasive technology is also directed at Goal 12: Develop noninvasive techniques for assessing the effectiveness of diet and physical fitness interventions.

Skeletal Muscle Response to Bed Rest and Cortisol Induced Stress, R. R. Wolfe, PI, University of Texas Medical Branch at Galveston, is testing an amino acid supplement designed to ameliorate muscle wasting induced by stress-and microgravity-induced depression of protein synthesis in a bed rest study. The study consists of 12 individuals with or without consumption of the supplement in a 30-day bed rest trial. A unique feature of this study is the use of a cortisol infusion at two times during the intervention period to mimic (in part) the documented elevated cortisol levels during space flight. Although primarily targeted to Goal 3: Reduce Risk of Diminution of Skeletal Muscle Function, we have considered this bed rest study to be our cornerstone project and have added a large number of ancillary grants which use the bed rest model and the nutritional intervention to address issues related to other goals. These "add on" projects will be discussed further in reference to Goal 14: Integrate Research and Analysis. To summarize here, separate projects working off of the Wolfe bed rest study are targeted to: Goal 1: Reduce Risk of Suboptimal Nutritional Status; Goal 2: Reduce Risk of Suboptimal Physical Fitness; Goal 3: Reduce Risk of Diminution of Skeletal Muscle Function; Goal 9: Reduce Risk of Depressed Immune Function; Goal 10: Reduce Risk of Loss of Bone Mineral Density; and Goal 14: Integrate Research and Analysis.

Nutritional Modulation of Pancreatic Endocrine Function in Microgravity, B. W. Tobin, PI, Mercer University School of Medicine, will determine amino acid countermeasure effects on endocrine function of human pancreatic islets of Langerhans with the goal to optimizing insulin synthesis and secretion under microgravity conditions. Dr. Tobin uses human pancreatic islet cells cultured on static plates or in a high aspect ratio vessel (HARV) designed to replicate some of the conditions of microgravity. The goal of this research project is to determine how different physiological conditions, characterized by over or under expression of certain hormones, affect insulin secretion and to develop an amino acid combination that will optimize this secretion. In becoming part of the Nutrition and Physical Fitness Team, Dr. Tobin has added a myocyte culture model to determine the effect of maximizing insulin secretion on muscle cell response. In addition to targeting Goal 1 (as do all nutrition based projects), this project specifically addresses Goal 3: Reduce Risk of Diminution of Skeletal Muscle Function, since uptake of amino acids into muscle is governed by insulin. Optimal insulin synthesis should maximize uptake of amino acids into muscle and thus enhance muscle protein synthesis. The other goal targeted by this research project is Goal 14: Integrate Research and Analysis. This goal will be described more fully later under Goal 14, but briefly stated, Tobin's project is using the amino acid levels found in blood of subjects from Wolfe's bed rest study who have received his amino acid supplement. Thus, there is integration between these two projects.

Treadmill Exercise as a Countermeasure for Microgravity Deconditioning, S. M. Schneider, PI, University of New Mexico, will evaluate, in flight, the effectiveness of two treadmill countermeasures to maintain aerobic capacity and leg strength, prevent increases in bone resorption and help prevent muscle atrophy. The anticipated countermeasure resulting from this research program will be an optimally designed treadmill, with a protocol that maximizes the above outcome measures, and is achieved with the least time expenditure. This research targets Goals 2, 3, 4, and 10.

Metabolic Adaptations of Skeletal Muscle to Training/Detraining. A Systems Model, M. E. Cabrera, PI, Case Western Reserve University, uses mathematical modeling to perform quantitative predictions of work capacity after periods of training/detraining. These models and predictive equations are based on data from animal and human studies and will provide a framework for quantitative understanding of the skeletal muscle metabolic adaptations to periods of training and detraining. Part of the database used in these predictive equations is nutritional information or metabolic status. Therefore, this research project serves to integrate nutrition and physical fitness and targets goals 1, 2, and 3, as well as, goal 14, integration.

We anticipate that the ground based research summarized above, combined with future projects discussed below, will eventually result in three fundamental countermeasure strategies to provide optimal nutrition and physical fitness, which in turn will ameliorate the risks shown in section 10.2. These general, broad-based strategies are summarized below.

1) *Development of the rationale and mechanistic justification for a combination of traditional and targeted functional foods which are highly palatable and designed to minimize the risks summarized in section 9.2, without negatively impacting either food intake or other risks for which they may not be specifically targeted.* For example, an amino acid supplement designed to enhance protein synthesis should not depress immune response or negatively impact bone health. A coordinated effort at the team level is required to achieve this goal. Some of these foods/supplements will be general to meet the nutrient requirements for all individuals in space. Others may need to be task specific, e.g. time-release energy foods for prolonged activity without additional food intake such as may be experienced during EVA. Although it is not the goal of the nutrition team to develop the foods and supplements, it is a team goal to determine the requirements for what should be in those foods/supplements.

2) *Development of an exercise protocol, and the appropriate equipment to maximize both muscle strength, lean body mass, bone strength, and aerobic capacity.* Studies will be designed

to determine the optimal as well as minimal prescription for frequency, duration, and intensity of the exercise countermeasure to obtain the most time efficient method to maintain muscle and cardiovascular capacity. Traditionally, this prescription is considered to involve two types of exercise protocols (resistance training and aerobic exercise), but where possible, their integration should be a priority. For example the Schneider project involves optimizing protocols for treadmill exercise. This form of exercise is typically considered an aerobic exercise, but properly structured with appropriate force and heel strike requirements; it may also contribute to leg muscle strength and potentially have a positive effect on bone strength (outcomes which are being tested with the proposed protocol). The overall intention of the physical fitness program is to produce the most physically fit individual (from both a strength and aerobic viewpoint) in the least amount of time. Since exercise takes time from other tasks and also requires energy input, which means greater food intake, accomplishing this task will have many benefits. In addition, the Nutrition and Physical Fitness Team is aware that different forms of preflight and in-flight physical exercise are a major countermeasure thrust for the Muscle Team and will work with the Muscle Team to coordinate and maximize the effectiveness of our collective programs to address shared goals.

3) *Development of a strategy of timing of food intake with respect to physical activity.* This countermeasure plan will be key to the overall health of individuals in space. Often overlooked, when one eats with respect to when one exercises has important consequences for overall utilization of nutrients and for human performance. The current recommendations for food intake timing with respect to exercise as practiced in flight are not based on strong scientific studies. A scientific basis for the timing of food intake and exercise prescriptions is needed. For example, R. Wolfe has shown in human studies, that providing amino acids prior to rather than after an exercise bout will enhance protein synthesis by up to three fold. Also, the appropriate combination of foods or new functional foods with time release components could provide a certain level of blood glucose over extended periods of time so that exercise or other tasks such as EVA could be performed without stopping to eat.

Keeping these three overarching countermeasure strategies in mind, the following is a discussion of the current status and future plans of the program with respect to the ten risk-based and four non-risk based goals defined in section 10.3. As noted above, goals 1 and 2 are considered central to all of the other goals. They are (1) Reduce Risk of Suboptimal Nutritional Status and (2) Reduce Risk of Suboptimal Physical Fitness. With respect to Goal 1, designing optimal diets for individuals in space is not just taking the recommended dietary reference intake values (DRIs) developed for Americans and Canadians and modifying them for microgravity conditions. Optimal nutritional status for maximal performance both in space and for optimal health after space flight has to be more than meeting minimal RDI requirements. One needs to ask the question, "Optimal for what?", and in this case it is for maintaining muscle strength, bone mass, immune function, etc. This fact means that all of the nutrition projects (Lupton, Wolfe and Tobin) are addressing various aspects of what would represent optimal nutrition – Lupton from a view towards protecting against radiation-enhanced cancer; Wolfe and Tobin from the viewpoint of maintaining muscle mass through amino acid uptake into muscle and appropriate insulin response. However, this view also means that many aspects of "optimal nutrition" are not currently being addressed. The most critical gap in meeting this goal is the absence of a program that deals with the anorexia of space flight. If one does not consume sufficient food, no matter how well designed the food is, the individual will not be nutritionally replete. Although clearly a multifactorial problem involving such diverse factors as psychosocial interactions, scheduling tasks, food palatability and ease of access and preparation, nausea and gastrointestinal disturbances, there appears to be a less clear, additional, causative factor induced by microgravity which is independent of other factors and results in diminished food intake. Alleviating this anorexia of space flight is a high priority for the Nutrition and Physical Fitness Team and was the basis for a listed priority item in the recent request for proposals in the last combined NASA/NSBRI funding announcement. The Team has benefited greatly from the combined expertise of Helen Lane and Scott Smith from NASA/JSC who know what has been tried in the past, what works and what does not work with respect to nutrition. These two individuals are on our team, are an integral part of our meetings and conference calls, and will assist in resolving this issue.

With respect to Goal 2 (Reduce Risk of Suboptimal Physical Fitness), again, development of successful countermeasures to meet this goal underlies all of the other goals. In many ways, there are already potential countermeasures at a high stage of development (exercise equipment and protocols) and with further relatively simple studies we could have countermeasures in place within a rapid time frame. The Schneider protocol is an example of such a study, which really tests the duration and intensity of treadmill exercise required to meet several "success" criteria. Studies such as this one will provide the scientific basis for exercise prescriptions. The Nutrition and Physical Fitness Team sees Goal 2 as being very practically oriented, rather than at the level of basic science. Protocols to be tested need to be ones that can be used in space and should aim towards the maximum benefits in the shortest amount of time. If funding for this team were increased, our next two subgoals within this goal would be: first, to have an exercise intervention which involves both aerobic and resistive training and second, to initiate a study designed to integrate exercise with diet (such as a study that would use the same protocol as the Wolfe bed rest study). This suggestion was also part of the request for proposals that went out in response to the combined NASA/NSBRI grants program in late 2001.

Goal 3 (Reduce Risk of Diminution of Skeletal Muscle Function) is the primary research focus of the current program, and four out of the five projects address this goal (Wolfe, Tobin, Schneider, Cabrera). The problem addressed is that muscular inactivity leads to decreased protein synthesis. This problem is compounded by the fact that stress (mediated by moderate hypercortisolemia) leads to increased protein breakdown. The combined effect of decreased synthesis and increased breakdown results in loss of skeletal muscle mass, which leads to loss of muscle strength. This compromises crew capabilities, including EVA or potential emergency egress. Countermeasures to these risks include an amino acid supplement designed to enhance protein synthesis (*Wolfe bedrest study)* which should also enhance insulin secretion and thus amino acid uptake into muscle and muscle synthesis (*Tobin, insulin secretion*). This dietary countermeasure, combined with an appropriate treadmill exercise should help maintain leg strength and aerobic capacity (*Schneider, treadmill)*, positively affecting both muscle strength and uptake of amino acids into muscle for protein synthesis. Finally, the newest addition to the team (*Cabrera, modeling adaptations of skeletal muscle*), will take data from the Wolfe, Tobin and Schneider programs and combine it with existing data from previously conducted research, to develop equations that will predict work capacity after periods of training/detraining. Progress towards achieving this goal is advancing, and the goal is adequately addressed by current research projects. In addition, as we more fully integrate with the Muscle Team (See Goal #14), our combined strengths in this area position us to advance rapidly through phases of countermeasure development.

Goal 4 (Reduce Risk of Reduced Cardiovascular Capacity) is partially addressed by the Schneider treadmill project. Additional aerobic exercise based protocols proposed by this team or others could serve to reduce further the risk of diminished cardiovascular capacity. The NSBRI cardiovascular team is also tackling various aspects of this problem directly. Given limited resources, therefore, our Team does not recommend a new project specifically targeted to cardiovascular capacity that is independent of enhancing aerobic capacity.

Goal 5 (Reduce Risk of Radiation Enhanced Development of Cancer) is currently being addressed by the Lupton project. Risks to personnel in space from radiation exposure are considered to be a tier one problem by NASA. A primary risk of radiation exposure is later cancer development. Of all the cancers, colon cancer is the second leading cause of death from cancer in the United States today. It strikes men and women equally. On the positive side, it is the cancer most amenable to diet intervention. Thus, studying mechanisms by which we can protect against the development of this cancer with respect to previous radiation exposure is important. To maximize our effectiveness in addressing this goal, future plans involve adding on projects to work off of the Lupton rat study, since rats irradiated at Brookhaven and kept through until tumor formation are a valuable resource that should be shared wherever possible. In addition, we plan to collaborate more closely with the Radiation Team in the future, in particular with Dr. Ann Kennedy, who also has a diet/radiation project using antioxidants.

Goal 6: Reduce Risk of Decreased Cognitive Function; Goal 7: Reduce Risk of Alterations in Sleep Patterns; Goal 8: Reduce Risk of Poor Psychosocial Adaptation are not part of the current program and are not anticipated to be part of the program in the near future. However, these are important risks, which are amenable to diet and/or exercise interventions. Nutrition and Physical Fitness are both interventions that affect all body systems and almost every risk. The challenge is to concentrate on those risks that have the best science base already established so that the NSBRI program can more rapidly achieve production of countermeasures. Goals 6,7 and 8 are at an early stage of scientific knowledge and therefore will be part of the program in the future rather than at this time.

Goal 9: Reduce Risk of Depressed Immune Function will not be addressed at this time. As mentioned above, the key risks of space flight to compromised immune function are being defined at this time. Therefore, the science is somewhat less mature than that for how muscle behaves during flight. For that reason, this goal will not be a primary area of research focus at this time. However, we currently have two projects related to this goal which are working off the Wolfe bedrest study: *(1) Effects of bed-rest on immune and inflammatory reaction and it's modulation by corticosteroids,* P. Uchakin, PI, Mercer University. Uchakin's hypothesis is that stress during inactivity alters the balance between cell-mediated and humoral immunity. *(2) Effects of prolonged bedrest on herpesvirus-specific immunity,* R. Stowe, PI, UTMB. The group's hypothesis is that prolonged bedrest will result in increased reactivation of latent herpes viruses.

Goal 10: Reduce Risk of Loss of Bone Mineral Density is addressed by a collaborative effort with R.Wolfe on the cornerstone bedrest study: *The effect of bed rest and amino acid supplementation on bone markers of calcium metabolism,* S. M. Smith, PI, NASA, JSC. Smith's hypothesis is that amino acid supplementation will reduce calcium excretion from bones via its effects on skeletal muscle.

The non risk-based goals are at various levels of development at this time. Goal 11: Monitoring Methods for Assessment of Food Intake and Physical Activity is being handled well by NASA but could be optimized with back up systems (for measuring exercise specifically). D. Hagan, Leader for exercise/physical fitness at NASA/JSC, is a member of our team, and we will work closely with him in the future to improve this monitoring system. Goal 12: Develop Noninvasive Technologies for Assessing the Effectiveness of Diet and Physical Fitness Interventions is in its infancy. One important aspect of the Lupton project is the use of microarray technology on mRNA from fecal material to see which genes are turned on or off during particular diet interventions, which ones are affected by radiation exposure, and how these gene array patterns predict for a variety of endpoints. This patented technique is well developed in the rat, and the plan is to later apply it to humans. As noted previously, diet and physical fitness interventions lend themselves very well to Earth-based applications (Goal 13). In particular, we envision a protein supplement that will enhance amino acid uptake into muscle and muscle protein synthesis as a result of the Wolfe bed rest study. This supplement will also be useful for individuals on Earth who have muscle wasting due to a variety of causes. We also envision a supplement of omega 3 fatty acids combined with pectin (a fermentable fiber) which may protect against both oxidative and alkylation damage to colonic DNA. With colon cancer the second leading cause of death from cancer in the US today, such a supplement could prove to be very beneficial. Modifications to a treadmill and developing strategies for simultaneously enhancing leg muscle strength along with aerobic capacity would also certainly be welcome for many people in the US who need to get the maximum benefit from exercise in the minimum amount of time.

Goal 14: Integrate Research and Analysis has already been a major part of the Nutrition and Physical Fitness Team. This goal includes efforts to enhance the interaction of individual Nutrition and Physical Fitness Team investigators: a) among the current team’s infrastructure, b) among investigators within other teams (eg. Muscle, Radiation Teams), and c) with investigators not formally associated with the NSBRI. The activities will allow us to greatly expand the resources of the NSBRI and the ability to tackle the risks of space travel. Table 10.2 summarizes our current efforts at integration. In addition to strong collaborations within our team, a few examples of integration of the Nutrition and Physical Fitness Team with other teams or researchers outside of the NSBRI are as follows: Lupton is collaborating with Judex (Bone Team) in supplying rat hind limbs from irradiated rats on different diets. The Wolfe bed rest study is a true collaborative effort with the following investigators/projects: P. Uchakin, Mercer University, testing the hypothesis that stress during inactivity alters the balance between cell-mediated and humoral immunity; S. M. Smith, NASA, JSC, The effect of bed rest and amino acid supplementation on bone markers of calcium metabolism; R.R. Fitts, Marquette University, The effect of prolonged bed rest and amino acid supplementation on muscle fiber function; and R. Stowe, UTMB, Effects of prolonged bedrest on herpesvirus-specific immunity. Similar measurements to the Stowe bedrest study are also being performed on the Shuttle and ISS crewmembers, and so the Stowe study would serve to complement in-flight work. Additional collaborative projects with the Wolfe study include: T.P. Stein, UMD-NJ, Does bed rest + hypercortisolemia lead to increased oxidative stress during the recovery phase?; H W Lane, NASA, JSC, The effect of bed rest and amino acid supplementation on muscle energy production during exercise. In addition to collaborative projects, several people who were not directly funded with NSBRI grants have become an active part of our team. They include Helen Lane and Scott Smith from NASA/JSC in the area of nutrition and Don Hagan, also NASA/JSC, in physical fitness. These close ties to NASA enable the Nutrition and Physical Fitness Team to be up to date on the most recent countermeasure approaches to addressing nutrition and physical fitness related risks.

10.5 OBJECTIVES AND STRATEGIC ACTIVITIES

Goal 1: *Reduce Risk of Suboptimal Nutritional Status*

Objective 1A. Assess Risk and/or Determine Level of Acceptable Risk

- Initiate a project that determines the metabolic basis of the anorexia of space flight if funds become available from NSBRI/NASA.
- Complete project to determine the combined effect of radiation and a colon carcinogen on the development of colon cancer and the level of risk caused by each type of DNA damage, individually and collectively (Lupton)

Objective 1B. Determine Mechanisms

- Complete project to determine effect of microgravity on insulin secretion and muscle metabolism (Tobin)
- Complete project to determine how and why specific diets protect against radiation and carcinogen induced DNA damage (Lupton)
- Complete project to determine if an amino acid supplement enhances protein synthesis during bed rest and cortisol infusion (Wolfe)

Objective 1C. Develop Countermeasures

- Complete project to develop diet intervention that ameliorates muscle wasting and therefore helps to reduce risk of suboptimal nutritional status (Wolfe)
- Complete project to develop fiber/fat supplement that ameliorates DNA damage (Lupton)
- Complete project that will develop the ideal ratio of amino acids to maximize insulin secretion and myocyte uptake facilitated by insulin which can later be made into a supplement (Tobin)

Goal 2: *Reduce Risk of Suboptimal Physical Fitness*

Objective 2A. Assess Risk and/or Determine Level of Acceptable Risk

Objective 2B. Determine Mechanisms

- Complete project to determine if treadmill exercise, properly configured, can also benefit bone health and muscle strength (Schneider).

Objective 2C. Develop Countermeasures

- Complete project to determine the optimal duration and intensity of treadmill exercise to ameliorate loss of muscle strength and loss of aerobic capacity (Schneider).
- If funding for this team were increased, determine the optimal combination of aerobic and resistance exercise, preferably in combination.
- If funding for this team were increased, integrate exercise with diet to determine the best combination with respect to both type and amount of food and exercise, and timing of one with respect to the other.

Goal 3: *Reduce Risk of Diminution of Skeletal Muscle Function*

Objective 3A. Assess Risk and/or Determine Level of Acceptable Risk

Objective 3B. Determine Mechanisms

- Complete project to determine effect of microgravity on insulin secretion and muscle metabolism and myocyte response (Tobin)

Objective 3C. Develop Countermeasures

- Complete project to develop diet intervention that promotes protein synthesis in muscle and ameliorates muscle wasting (Wolfe)
- Complete project to develop optimal physical fitness protocols for space that will serve to maintain skeletal muscle function (Schneider)

- Develop equations that can be used to predict for work capacity after periods of training/detraining (Cabrero)
- Working with the Muscle Team, integrate the proposed countermeasures between teams

Goal 4: *Reduce Risk of Reduced Cardiovascular Capacity*

Objective 4A. Assess Risk and/or Determine Level of Acceptable Risk

Objective 4B. Determine Mechanisms

Objective 4C. Develop Countermeasures

- Complete project to develop optimal physical fitness protocols for space (Schneider)

Goal 5: *Reduce Risk of Radiation Enhanced Development of Cancer*

Objective 5A. Assess Risk and/or Determine Level of Acceptable Risk

- Complete project to determine the additive or synergistic effect of radiation and a colon specific carcinogen on tumor development (Lupton)

Objective 5B. Determine Mechanisms

- Complete project to determine how radiation and carcinogen result in greater DNA damage than either alone (Lupton).
- Complete project to determine how diet is protective against the development of radiation-enhanced colon carcinogenesis (Lupton)

Objective 5C. Develop Countermeasures

- Complete project to develop diet intervention that protects against radiation-induced cancers (Lupton)

Although the next three goals (6,7,8) represent important risks, which are amenable to diet and/or exercise interventions, a stronger science base is required before we can effectively target countermeasures to these risk areas. For that reason the Nutrition and Physical Fitness Team does not have specific strategic activities in support of these goals at this time.

Goal 6: *Reduce Risk of Decreased Cognitive Function*

Objective 6A. Assess Risk and/or Determine Level of Acceptable Risk

Objective 6B. Determine Mechanisms

- Initiate a project to determine how diet and/or exercise could potentially ameliorate the risk of decreased cognitive function. This would be possible if funding became available

Objective 6C. Develop Countermeasures

Goal 7: *Reduce Risk of Alterations in Sleep Patterns*

Objective 7A. Assess Risk and/or Determine Level of Acceptable Risk

Objective 7B. Determine Mechanisms

- Initiate a project to determine how diet and/or exercise could potentially ameliorate the risk of alterations in sleep patterns. This would be possible if funding became available

Objective 7C. Develop Countermeasures

Goal 8: *Reduce Risk of Poor Psychosocial Adaptation*

Objective 8A. Assess Risk and/or Determine Level of Acceptable Risk

Objective 8B. Determine Mechanisms

- Initiate a project to determine how diet and/or exercise could potentially ameliorate the risk of poor psychosocial adaptation. This would be possible if funding became available

Objective 8C. Develop Countermeasures

Goal 9: *Reduce Risk of Depressed Immune Function*

Objective 9A. Assess Risk and/or Determine Level of Acceptable Risk

Objective 9B. Determine Mechanisms

- Complete project to determine how bed rest and corticosteroids affect immune and inflammatory reactions (Uchakin, collaboration with Wolfe).
- Complete project to determine if prolonged bedrest will result in increased reactivation of latent herpesviruses (R. Stowe, collaboration with Wolfe).

Objective 9C. Develop Countermeasures

Goal 10: *Reduce Risk of Loss of Bone Mineral Density*

Objective 10A. Assess Risk and/or Determine Level Of Acceptable Risk

Objective 10B. Determine Mechanisms

Objective 10C. Develop Countermeasures

- Complete project to develop optimal physical fitness protocols for space (Schneider)
- Complete project to determine if the amino acid supplement in the Wolfe bedrest study also ameliorates loss of bone mineral density (S. M. Smith, collaboration with Wolfe).

Goal 11: *Develop Monitoring Methods for Assessment of Food Intake and Physical Activity*

- Work with NASA/JSC to optimize monitoring methods

Goal 12: *Develop Noninvasive Techniques for Assessing the Effectiveness of Diet and Physical Fitness Interventions*

- Complete project to determine which changes in gene expression predict for later tumor development (Lupton) in rats.
- Using these markers (noted above) optimize protocols for their applications to humans.

Goal 13: *Develop Earth-based Applications for Diet and Physical Fitness Interventions*

Objective 13A. Develop a protein supplement that will enhance amino acid synthesis and can be used in conditions of muscle wasting.

Objective 13B. Develop an omega 3/fiber combination supplement that may be used to protect against colon cancer.

Objective 13C. Develop appropriate modifications and exercise prescriptions for treadmill exercise that may benefit individuals both aerobically and with respect to strength.

Goal 14: *Integrate Research and Analysis*

Objective 14A. Integrate Research Within the Nutrition and Physical Fitness Team.

- Continue current integration efforts among the Nutrition and Physical Fitness Team investigators as summarized in Table 10.2.
- Use Wolfe amino acid supplement in Tobin project and complete both projects
- Complete collaborative project between Wolfe and Uchakin (part of Tobin project) to determine the impact of amino acid supplement and bedrest on immune response.

- Use data from all projects within the team to become part of the mathematical modeling project and complete modeling project (Cabrera)

Objective 14B. Integrate Research With Other Teams, Using Modeling as well as Other Approaches.

- Complete synergy project between Lupton (Nutrition) and Judex (Bone).
- Use of common diet and exercise protocols

Objective 14C. Integrate Research with Scientists Outside of NSBRI

- Complete integrative project between Wolfe bedrest study and S. M. Smith, NASA/ JSC, on the effect of amino acid supplementation on bone markers of calcium metabolism.
- Complete collaborative project with R.R. Fitts, Marquette University, and the Wolfe bedrest study on the effect of prolonged bed rest and amino acid supplementation on muscle fiber function.
- Complete collaborative project with R Stowe, UTMB, and the Wolfe bedrest study on the effects of prolonged bedrest on herpesvirus-specific immunity. These measurements are also being performed on the Shuttle and ISS crewmembers and would serve to complement in-flight work
- Complete collaborative project with the Wolfe study and T.P. Stein, UMD-NJ, on whether or not bed rest + hypercortisolemia leads to increased oxidative stress during the recovery phase.
- Complete collaborative project with the Wolfe study and H W Lane, NASA, JSC, on the effect of bed rest and amino acid supplementation on muscle energy production during exercise
- Continue collaborative partnerships with H. W. Lane, S. M. Smith and D. Hagan at NASA/JSC to seek out areas in which we can work together towards common goals.

10.6 SUMMARY

In the next 3-5 years, the Nutrition and Physical Fitness Team should be able to implement both the fundamental and applied research programs that address the identified risks outlined in this Research Plan. As discussed in the plan, the primary unifying goal at the onset is to develop countermeasures to diminution of skeletal muscle function (Goal 3). Four of our five currently funded projects are targeted to this goal. One of these projects will allow us to understand, mechanistically, how bed rest and heightened cortisol levels affect muscle protein synthesis and how an amino acid supplement can ameliorate the risks of muscle atrophy. From the second project, we will understand at a basic level the amino acid requirements for efficient insulin synthesis and secretion, and how insulin secretion can be optimized with an appropriate amino acid supplement. Adding to our applied outcome knowledge base will be information from the third project, which will delineate how often and what intensity treadmill exercise is required to maintain leg muscle strength and aerobic capacity (also achieving Goal 4). Finally, our mathematical modeling project will take data from the three projects mentioned above, plus other NSBRI projects and research in the literature, and develop predictive equations to determine, in advance, how an individual in space will perform (from a metabolic and fitness viewpoint) when following a specific exercise regimen. The integration (Goal 14) of these four projects towards this common goal is shown in Figure 10.1. This focus on muscle function will also serve to help meet our first two goals, which involve optimizing nutritional status and physical fitness. Earth-based benefits will be generated from the projects targeted to maintaining muscle mass and strength (Goal 13). Such benefits include appropriate foods/supplements to enhance protein synthesis in muscle wasting states and to optimize muscle strength using exercise protocols. The timeline for accomplishing the tasks targeted to Goal 3 are shown in Table 10.3.

Another major accomplishment envisioned during this time frame is an understanding of the mechanism by which radiation exposure and exposure to a carcinogen can interact to promote colon cancer development (Goal 5). Further, the nutritional countermeasure to combat DNA damage from radiation will be identified and established with sufficient substantial data to justify a human clinical application.

In addition, one of the most significant accomplishments over the next five years will be the combined findings of the seven ancillary projects that are using the Wolfe bed rest study as their source of material. Figure 10.2 shows the synergistic nature and areas of research that will be completed using the same subjects and intervention protocol of the Wolfe study. Not only will these results provide important data independently, but also the fact that they all use the same subjects and interventions will provide a rich database for comparisons between the outcome variables. At the end of this study, we will know not only how and if an amino acid supplement protects against depressed protein synthesis but also how this intervention affects immune response, muscle fiber type, markers of bone health, oxidative stress and muscle energy production.

The overarching aim of the NSBRI Nutrition and Physical Fitness program is to provide diet/functional food/supplement countermeasures which optimize nutritional status and exercise countermeasures which optimize physical fitness that, when combined, maximize the effectiveness of each.

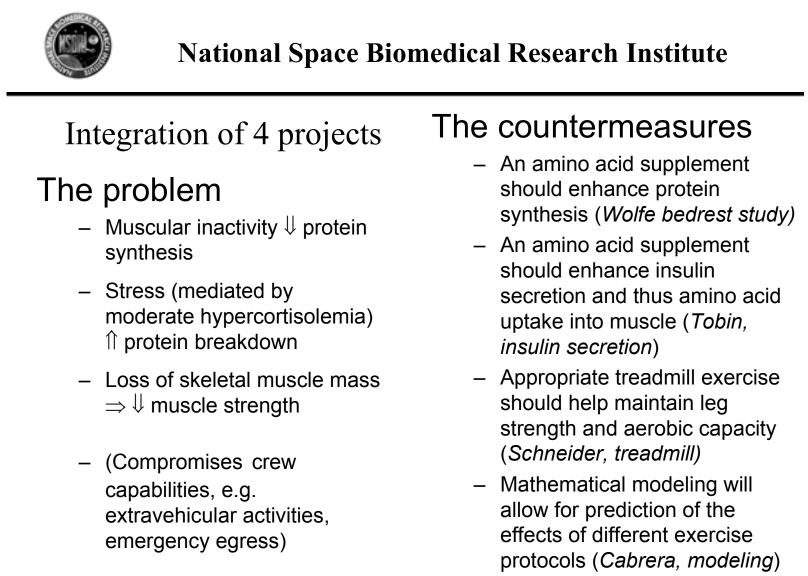

Figure 10.1. This figure illustrates the integration of four of the five currently funded projects that are targeted towards the common goal of maintaining muscle mass and strength

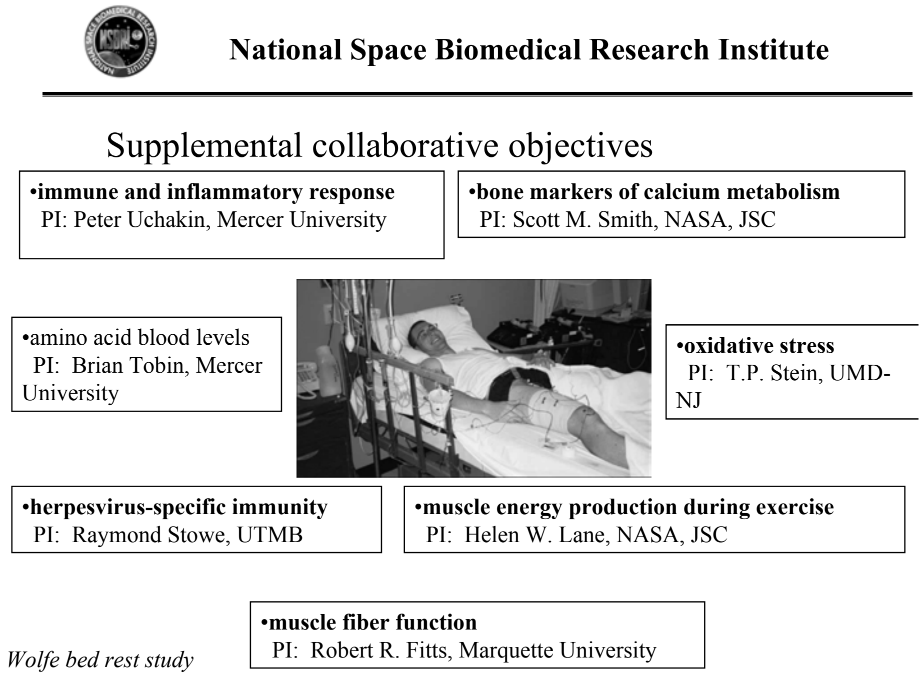

Figure 10.2. Synergy projects based on the Wolfe bed rest study

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Table 10.1. Project Research Activities

PI/Project	Risk(s) Addressed	Countermeasure Target	Experimental System	Phase 1 Activities: Focused Mechanistic Research	Phase 2 Activities: Preliminary Countermeasure Development Research	Phase 3 Activities: Mature Countermeasure Development Research
CABRERA/Metabolic Adaptations of Skeletal Muscle to Training/Detraining. A Systems Model	Diminished muscle function	Exercise	Computer Simulations and experimental data on rats and humans	Integrate existing knowledge into computational models of muscle metabolism	Predict effects of muscle mass loss and changes in fiber type distribution on muscle metabolism	Predict effects of detraining and/or exercise training on metabolism and work capacity
LUPTON/Nutritional Countermeasures to Radiation Exposure	Radiation-induced carcinogenesis	Diet/Nutrition	Rat	Test diets in rats injected with a colon specific carcinogen with/without radiation exposure to see which diet is protective against radiation and methylation damage, and how it protects	Predict effects of the optimal diet at each stage of the tumorigenic process and optimize noninvasive recovery of mRNA from exfoliated colon cells to predict and monitor the tumorigenic process	Develop and test dietary supplements that will decrease oxidative and methylation damage to colonic DNA and monitor their effectiveness through a noninvasive technique
SCHNEIDER/Treadmill Exercise as a Countermeasure for Microgravity Deconditioning	• Reduced cardiovascular capacity • Loss of bone • Diminished muscle function	Exercise	Human in flight study	Test different treadmill exercise protocols for maximal effectiveness in maintaining aerobic capacity, muscle strength, and bone mass	Evaluate effectiveness of exercise intervention protocols as related to outcome measures such as ability to do work	Integrate exercise protocols with nutrition protocols for maximum effectiveness
TOBIN/Nutritional Modulation of Pancreatic Endocrine Function in Microgravity	Diminished muscle function	Diet/Nutrition	Cultured pancreatic islet cells (HARV)	Determine nutrient needs of human pancreatic islet cells under different hormonal conditions designed to mimic microgravity and stress	Develop a nutrition intervention to ameliorate the depressed insulin secretion from human pancreatic islet cells	Test the diet intervention strategy in a bed rest/cortisol stressed research program
WOLFE/Skeletal Muscle Response to Bed Rest and Cortisol Induced Stress	Diminished muscle function	Diet/Nutrition	Human bed rest	Determine if a glucose /amino acid supplement provided during bed rest helps to ameliorate depressed protein syn-thesis, muscle wasting & loss of muscle strength	Optimize the supplement and the timing of the supplement with respect to exercise	Formulate the supplement for timed release, palatability, etc.

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Table 10.2. Integration Activities

	CABRERA	LUPTON	SCHNEIDER	TOBIN	WOLFE
Internal Communication	Entire team at meetings and telecons	Entire team at meetings and telecons	Entire team at meetings and telecons	Entire team at meetings and telecons	Entire team at meetings and telecons. P. Uchakin from Tobin project is now situated in Wolfe lab.
Integrated Experiment Development	Integrate existing knowledge into computational models of muscle metabolism using data from nutrition and physical fitness, the literature, and the muscle team	Uses the same strain of rat and the same radiation protocol at Brookhaven National Lab as does the Dicello rat long term studies (Radiation Team). Thus results can be compared.	As a result of team meeting discussions, specific outcome measures of muscle strength will be added that can be related to outcomes from Wolfe study. Diet intake will be monitored.	Tobin has redesigned his research protocol as a result of talks with team members to now include myocyte cultures and is also using blood from Wolfe study to determine levels of amino acids to use in his cell culture system. Uchakin, a CoI with Tobin, is now collabor-ating directly with Wolfe	This bed rest study is highly integrated with a variety of projects. The same amino acid supplement is tested in the Tobin project and we plan to have it tested in the Baldwin rat model (Muscle Team).
Sample Sharing	Data from Wolfe, Lupton, Schneider, Baldwin (muscle team) and others from muscle team	Tobin will use pancreas from Lupton rats. S. Judex (bone team) will use rat hindlimbs, H. Hogan, TAMU, will also use bones.	Data from the experiment will be shared with Cabrera for his prediction models	Will use pancreas from Lupton, will provide pancreatic cells to R Walzem, TAMU, for lipid analysis	There are currently seven "add on" projects to the bed rest study . See discussion of Goal 14 in this report.
Synergistic Studies of Opportunity	Aerobic and resistance exercise training with humans, and applying this to his model	Planned integration with A. Kennedy of radiation team for potential cross-use of each other's diet interventions	Planning with Schneider (who is doing bed rest studies) to have a uniform diet protocol	Future goal is to fly the HARV with pancreatic cells in space to determine how well the results mimic his system on earth	This study maximally capitalizes on synergistic opportunities which have arisen in the course of meetings and telecons to expand the program with "add on" grants.
Development of Computer Model of Integrated Human Function	This is exactly what the project is and should be an integrating force for the entire team.	Data from this project will be used by Cabrera for his prediction equations.	Data from this project will be used by Cabrera for his prediction equations	Currently this research is all ex vivo and not suitable for the integrated function component which we are only doing in animals and humans	Data from this project will be used by Cabrera for his prediction equations

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Table 10.3. Achieving Goal 3: Reduce Risk of Diminution of Skeletal Muscle Function

Countermeasure Development Phases	Pre 2001	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
Phase 0: Observational & Phenomenological Research													
Phase 1: Focused Mechanistic Research													
• Understand muscle protein synthesis under bed rest/cortisol enhanced conditions • Determine the amino acid requirements for muscle protein synthesis													
• Determine the amino acid requirements for insulin secretion under various stress-enhanced conditions (*in vitro* HARV) • Determine the proper ratio of amino acids to enhance uptake into myocytes													
Phase 2: Preliminary Countermeasure Development Research													
• Test amino acid supplementation and how this may promote muscle protein synthesis in humans													
• Study role of amino acid supplements as countermeasure strategy (combining results from Wolfe and Tobin) • Develop predictive equations for estimating work performance as a result of different exercise paradigms													
Phase 3: Mature Countermeasure Development Research													
• Test different protocols to optimize muscle strength and aerobic capacity in space (Schneider) • Develop integrated exercise and nutritional countermeasure and test in humans													
Phase 4: Countermeasure Evaluation & Validation													
• Testing of integrated exercise and nutritional interventions inflight • Test ability of theoretical predictive equations to actually predict for work performance in humans, in space													
Phase 5: Operational Implementation of Countermeasure Strategy													