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Exploration-Related Research on ISS: Connecting Science Results to Future Missions

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Abstract

In January, 2004, the U.S. President announced *The Vision for Space Exploration*, and charged the National Aeronautics and Space Administration (NASA) with using the International Space Station (ISS) for research and technology targeted at supporting U.S. space exploration goals. This paper describes:

- What we have learned from the first four years of research on ISS relative to the exploration mission,
- The on-going research being conducted in this regard, and
- Our current understanding of the major exploration mission risks that the ISS can be used to address.

Specifically, we discuss research carried out on the ISS to determine the mechanisms by which human health is affected on long-duration missions, and to develop countermeasures to protect humans from the space environment. These bioastronautics experiments are key enablers of future long duration human exploration missions. We also discuss how targeted technological developments can enable mission design trade studies. We discuss the relationship between the ultimate number of human test subjects available on the ISS to the quality and quantity of scientific insight that can be used to reduce health risks to future explorers. We discuss the results of NASA's efforts over the past year to realign the ISS research programs to support a product-driven portfolio that is directed towards reducing the major risks of exploration missions.

The fundamental challenge to science on ISS is completing experiments that answer key questions in time to shape design decisions for future exploration. In this context, exploration-relevant research must do more than be conceptually connected to design decisions—it must become a part of the mission design process.

1 Introduction

While NASA has always engaged in space exploration research, *The Vision for Space Exploration* [1] has brought with it specific mission definitions, corresponding timelines, and focused research objectives. The International Space Station is a key element in supporting this focused research. What may not be evident is the amount of ISS scientific research and development that is targeted towards exploration objectives. We have arranged our discussion topically so that the reader can understand accomplishments and progress in each area of research. We devote the beginning of each topical section to discussion of what has been learned and the latter portion of each section to what is currently on-going in this regard. Also, the short-hand name or acronym for each experiment is in bold text for ease of use.

Prior to the announcement of *The Vision for Space Exploration*, NASA, along with the International Partners, had envisioned the ISS as a “world-class” microgravity laboratory available to a broad-based user community spanning academic, industrial, commercial and educational elements [2]. Indeed, the breadth of the potential user community that NASA had courted was often cited as a source of resulting disenfranchisement for those who had committed resources to the use of ISS (e.g., [3]). Research objectives for ISS ranged from the pursuit of basic, fundamental scientific understandings of microgravity physics, to targeted commercial technology developments. While this range encompassed the research necessary to further space exploration, *The Vision for Space Exploration* and subsequent definition of specific missions for NASA have included a much more focused use of the ISS. Human health research efforts on ISS

have been guided by the *Bioastronautics Roadmap* [4], a synopsis of the risks of space exploration to human health (on ISS, reference lunar, and reference Mars exploration missions) and the research questions that need to be addressed to reduce these risks. NASA is now evolving specific research mission objectives to accomplish on ISS within a specific timeframe. Section 3 of this article addresses the approach to determine how the ISS can be used to address specific, targeted risks to human health on long-duration exploration missions.

In addition to the focus on human health, NASA is beginning to address technology development issues for exploration missions. Experiments to improve environmental monitoring, fire detection and suppression, and inspection and repair techniques will provide information critical for exploration vehicle designs.

The ISS can be viewed as an experiment in and of itself in many respects, as it is a unique, one-of-a-kind space vehicle. We note that ISS achievements are not limited to the scientific research discussed in this paper and refer the interested reader to broader treatments of the engineering, operational, and human accomplishments from the International Space Station [5, 6, 7, 8] in order to understand the full scope of the contribution of ISS to the path of evolution of NASA's exploration objectives.

2 Exploration Research Results and Current Exploration Investigations

Research on ISS began in 2000. As of this writing, Expedition 11 is underway, and twenty eight astronauts and cosmonauts have occupied the ISS on long-duration missions (i.e., 4 to 6 month Expeditions). Research on-board is planned within mission constraints such as astronaut availability as test subjects and test conductors, ability to launch and return experiments on U.S. and International Partner vehicles, and conditioned stowage availability (e.g., freezers). (A current overview of these constraints can be found in [9].) Most of the experiments on ISS require multiple Expeditions for completion; in particular, human research studies require specific numbers of test subjects for statistically meaningful results. As a result, experiments are in various stages of completion: some are nearing completion, some have just been initiated, and some are on hold awaiting availability of the Space Shuttle [9].

2.1 Physiology in Microgravity: Bone and Muscle

When astronauts spend months in a microgravity environment, they experience significant physiological changes. The effects on bone, muscle, and calcium mobilization in the body were discovered in the Skylab program [10], studied incrementally during relatively short Space Shuttle missions [11], and have been a focus of study since the beginning of ISS research. The transit to Mars from Earth will be equivalent in duration to the typical 6-month ISS Expedition. This allows us to draw insight into the health status that can be expected when a crew lands on Mars.

The primary countermeasure to loss of bone and muscle while on ISS has been exercise¹. Exercise equipment deployed on ISS is more mature and the prescribed exercise regimens are more rigorous than for any previous U.S. spaceflights. Early ISS studies have evaluated effects of long-duration spaceflight on bone and muscle in the context of these exercise protocols. The

¹ Exercise influences outcomes in systems beyond bone and muscle (i.e., cardio-vascular), but we see the most directly attributable results of exercise in bone and muscle, so choose to address it here.

performance of exercise hardware on orbit has not been ideal, and we include an annex to this paper that describes the state of the exercise hardware on board ISS (Annex 1).

The study, *Sub-regional Assessment of Bone Loss in the Axial Skeleton in Long-Term Spaceflight (Sub-regional Bone)*, Thomas F. Lang, University of California, San Francisco), determined the distribution of bone loss in the spine and hip in long-duration spaceflight using quantitative computed tomography (QCT) and assessed how bone is recovered after return. One of the first bioastronautics research investigations to begin on ISS, this study recruited 14 subjects between Expedition 2 through Expedition 6. At least 8 subjects have been back long enough for investigators to have also measured their bone density one year post flight [12] to assess recovery. On ISS, bone mineral density was lost at an average rate of about 0.9% per month in the lumbar spine and 1.4% per month in the femoral neck [13]. For comparison, a post-menopausal woman experiences losses of bone mineral on the order of 1% per year (e.g. [14]). The experiment provides insight into the process of bone loss because it is the first study to differentiate the loss in the cortical bone (the outer part of the bone) and the trabecular bone (the inner parts of the bone). For example, in the hip, losses of mass in the cortical bone averaged around 0.5%/month whereas losses in the trabecular bone averaged 2.5%/month [13]. Post-flight measurements of bone recovery will soon be complete. These results were from crewmembers who were participating in typical U.S. spaceflight exercise regimens; albeit with exercise routines for some subjects compromised by hardware failures (see Annex 1). Now that we better understand the distribution of bone loss, development of countermeasures to control these regional losses is paramount to assure successful human exploration. If Mars mission design includes a zero gravity transit, these countermeasures will be critical to insure that crewmembers are physically capable of completing tasks on Mars and making a safe return. Should an artificial gravity mission design be selected for Mars transit, this understanding of bone loss forms the foundation for gravity prescriptions during transit.

Effects of Altered Gravity on Spinal Cord Excitability (H-Reflex): Doug Watt, McGill University, Montreal, Canada. This study of spinal cord excitability using the Hoffman reflex was conducted during Expeditions 2-4. The study found that spinal cord excitability decreased by about 35% in weightlessness, and then stayed at the new level for the duration of the mission. It then took about 10 days back on Earth for astronauts to fully recover their muscle strength and spinal cord excitability [15,16]. This difference in excitability means that only a portion of muscle fiber units are contracting in response to signals from the nervous system, and explains functionally why muscle mass declines in weightlessness, even with exercise. The reduced excitability means that there might be limits on the degree to which heart muscle strength, leg muscle tone, and even bone density (for which muscle contraction is an important regulating factor) can be maintained through exercise on long-duration missions [16]. Because this decrease in excitability is only observed on orbit and not in bed rest (an analogue for weightless space travel), the results highlight the possibility that reduced excitability with corresponding loss of muscle and bone, might be partly a nervous system response and not simply due to disuse of the legs [15, 16]. Decreased spinal cord excitability could thus be an issue for long duration stays in partial gravity environments such as the moon and Mars, and future exercise devices could provide feedback on work actually performed to help crewmembers compensate for decreases in exercise efficiency [15].

Currently on ISS, loss of muscle mass during long-duration spaceflight is being studied from several perspectives. The route of directly observing changes in muscle fibers by comparing them before and after flight is used in *Effect of Prolonged Space Flight on Human Skeletal Muscle (Biopsy)*, R. Fitts, Marquette University). Tests of hand and arm strength are used in a

study called *Hand Posture Analyzer (HPA)*, V. Zolesi, Italian Space Agency). Measurements of mechanical loads in the joints of the lower extremities are the focus of *Foot/Ground Reaction Forces during Space Flight (Foot)*, P. Cavanaugh, The Cleveland Clinic). Each of these experiments requires additional subjects before completion in order to provide statistically meaningful results.

Previous studies related to *Biopsy* on Space Shuttle astronauts and *Mir* cosmonauts (reviewed by [17]) have identified muscle atrophy and changes in the muscle contractile proteins, with the potential for damage to fibers on return to gravity. Analysis of preliminary data from 5 observations of ISS crewmembers confirms this pattern [18]. *Biopsy* was initiated during ISS Expedition 5, and is scheduled for completion after Expedition 11. Data will determine the structural and metabolic changes that occur within individual muscle fiber cells. Preliminary results suggest that of the exercise countermeasures currently being employed (treadmill, resistive exercise, and cycle ergometer, Fig 1), extensive (> 200 min/week) treadmill exercise was more effective than other exercise modalities in protecting the calf muscles [19]. Preliminary results also indicate that although in-flight countermeasure exercise does reduce the amount of muscle atrophy and strength loss, loss of muscle mass and corresponding loss muscle power of 13-51% occurred during a 6-month stay on ISS [20]. With repaired exercise equipment and the additional subjects scheduled through ISS Expedition 11, continued results from this experiment should help determine the adequacy of current exercise countermeasures in reducing the risks from loss of muscle mass for planning future exploration missions.

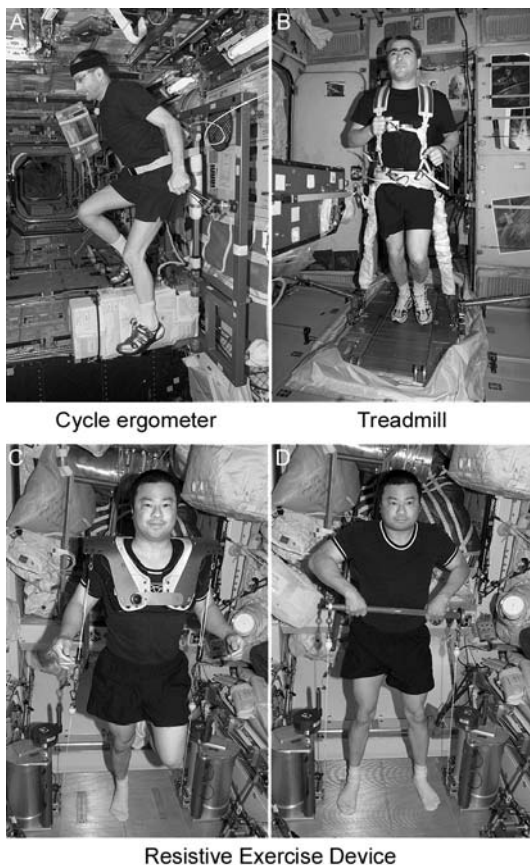


Figure 1. Exercise modalities on ISS.

A. Astronaut Donald R. Pettit uses the Cycle Ergometer with Vibration Isolation System (CEVIS) in the Destiny laboratory, ISS006-E-13965, 2 January 2003.

B. Cosmonaut Salizhan S. Sharipov, equipped with a bungee harness, exercises on the Treadmill Vibration Isolation System (TVIS) in the Zvezda Service Module, ISS010-E-05609, 31 October 2004.

C. Astronaut Leroy Chiao, wearing squat harness pads, exercises using the Schwinn Resistive Exercise Device (SchRED) equipment in the Unity node, ISS010-E-05325, 28 October 2004.

D. Chiao uses the short bar on the SchRED to perform upper body strengthening pull-ups, ISS010-E-05343, 28 October 2004.

HPA examines the way hand and arm muscles are used differently during grasping and reaching tasks in weightlessness. Measurements are compared to those taken before and after flight to improve understanding of the effects of long duration spaceflight on muscle fatigue. *HPA* was first used on board the ISS during the "Marco Polo" Soyuz taxi flight of astronaut Roberto Vittori in 2002. Studies of long-term effects of weightlessness on the upper limb performance were carried out during ISS Expeditions 7 and 8 and the experiments were continued by a visiting Soyuz taxi crewmember at the beginning of Expedition 11. The first protocol completed using *HPA* equipment, *CHIRO* (Crew Health Investigation for Reduced Operability), is planned to be supplemented with additional experimental protocols [21]. Results could help in planning the manual tasks that might be required of future long duration crewmembers.

A biomechanical approach to measuring mechanical loads on the lower extremities is being used in the *Foot* experiment. *Foot* characterizes the load placed on legs and feet during daily activities on the ISS. Each participating crewmember is instrumented with sensors—a calibrated force-sensing shoe insole, joint sensors that record angles at the ankle, knee, and hip, and electrodes to record muscle activity in leg muscles. Once actual on-orbit loads are understood, more efficient and focused countermeasures to bone and muscle loss (such as better exercise regimens or equipment) can be developed for exploration missions. The experiment has been conducted on three subjects to date, on Expeditions 6, 8, and 11, with additional subjects planned for Expedition 12. Preliminary results have already given us great insight into why bone is being lost by crewmembers during their stay on ISS in spite of the exercise protocols in place. Peak forces experienced during treadmill runs were approximately 63% of the forces that would have been experienced running on a treadmill on Earth. During 161 days in orbit, bone was lost at a rate of 0.72% and 2.31% per month in the total hip and lumbar spine regions, respectively [22], and similar to bone loss documented by the *Sub-regional Bone* experiment [13].

The loss of calcium from bone combined with decreased fluid intake in flight increases the probability for renal stone formation during and after flight. Both factors increase the likelihood that solid particles will condense in the kidneys [23]. Information on kidney stone formation is closely held due to medical privacy, but it is known that through 2001, 14 astronauts have experienced kidney stone formation post-flight [24] while few in-flight kidney stones have been documented. Since access to medical care is limited aboard spacecraft, occurrence of renal stones in a crewmember could endanger mission objectives. Renal stones can cause acute debilitating pain prior to passage, and if a blockage occurred that could not be surgically treated, become life-threatening. A countermeasure study, *Renal Stone Risk During Spaceflight: Assessment and Countermeasure Validation (Renal Stone)*, Peggy Whitson, NASA Johnson Space Center) is using pharmaceutical administration of potassium citrate (10 mg daily in flight) to reduce the probability of renal stone formation. The protocol was designed to be double-blinded and placebo controlled. Effectiveness of the potassium citrate is assessed using chemical analysis of 24-hr urine collection samples. The experiment was conducted on Expeditions 3-6, 8 and 11, and is planned to continue on Expeditions 12-14.

When ISS research results are combined with data from previous studies on Shuttle and the *Mir* Space Station, and with analog bed-rest studies conducted on Earth, we are developing a better understanding of how microgravity affects bone and muscle. To summarize: the lack of gravitational force means that muscles are not used every moment as they are on Earth, and muscles begin to weaken. The reduced activity of muscles against bone puts the natural processes of bone renewal out of balance, leading to significant bone losses. Mobilization of calcium from the net bone loss increases the risk of kidney stones.

In spite of the reasonable understanding of the effect of microgravity on bone, muscle and calcium mobilization, and the history of exercise prescriptions and countermeasures tested, a clear set of clinical recommendations for preventing bone and muscle loss during long-duration exploration missions remains to be tested and confirmed on ISS (see also Annex 1). What we do know is that exercise equipment is important for maintaining crew health and function during even shorter duration flights. A pharmacological countermeasure might need to be combined with exercise in order to maintain bone during a Mars mission [25], and ISS will likely be the only opportunity to prove a set of combined countermeasures on a long-duration flight before a human transit to Mars.

2.2 Physiology in Microgravity: Adaptation to Changes in Gravity

When astronauts move between different gravity environments (e.g., ISS to Earth, Earth transit to Moon, or Earth transit to Mars) a number of acute physiological responses can affect their health and performance. When first experiencing microgravity conditions in Earth orbit, some crewmembers experience short-term space motion sickness which impacts their ability to complete tasks in the early days of a mission. Following spaceflight, orthostatic intolerance (the inability to regulate blood pressure while upright) can occur, which can cause syncope (sudden fainting). Also following spaceflight, simple locomotor function (e.g., walking and standing upright) can be impaired. The magnitude and duration of post-flight sensorimotor disturbances, including orthostatic intolerance, increases with longer duration missions [26]. These disturbances pose a risk to crew safety and to mission objectives if nominal or emergency vehicle egress is required following long duration missions (e.g., landing on Mars).

No present operational countermeasures exist for these problems on return to gravity, and the degree to which there would be post-flight sensorimotor disturbances following transit to and landing on Mars is unknown. However, most mission scenarios envision 6-month transit times and post-flight disturbances would likely be similar to those observed after ISS missions. Thus, ISS is currently a test bed for a number of methods for improving adaptation to changes in gravity.

Xenon 1 examined the mechanisms of vascular responses to microgravity and was among the first experiments completed on ISS. The *Mobility* experiment is examining in-flight countermeasures to increase adaptation on return to gravity. The *Midodrine* experiment is evaluating use of an approved drug to counter orthostatic intolerance upon landing. The *PMZ* experiment is enhancing our understanding the space motion sickness drug Promethazine and its pharmacology in microgravity.

In the *Effect of Microgravity on the Peripheral Subcutaneous Veno-Arteriolar Reflex in Humans (Xenon1)*, A. Gabrielsen, Danish Aerospace Medical Center of Research National University Hospital (Rigshospitalet), Denmark), a ¹³³Xenon radioactive tracer was used to visualize subcutaneous blood flow to monitor the function of the veno-arteriolar reflex (the mechanism in the body that prevents blood from pooling in the feet). The experiment was completed on Expeditions 3-5, and preliminary analysis indicates that the veno-arteriolar reflex continues to function normally in microgravity (Anders Gabrielsen, personal communication).

Promoting Sensorimotor Response Generalizability: A Countermeasure to Mitigate Locomotor dysfunction After Long-Duration Space Flight (Mobility), J. Bloomberg, NASA Johnson Space Center, Houston, TX). The countermeasure approach chosen in this investigation utilizes the ISS treadmill and adds an in-flight training regimen to enhance adaptive generalization of locomotor

function, facilitating rapid and robust recovery of functional mobility after long-duration spaceflight. The concept employs variable practice and task variation as a training technique to enhance motor learning ability and generalization to other task constraints and environments. Variable practice enhances the ability of the performer to learn a novel motor task. The subject learns to solve a class of motor problems, rather than a specific motor solution to one problem. This study will manipulate the conditions of exercise (load and speed) and incorporate alterations in visual flow during treadmill exercise by showing different visual stimuli on a large display in front of the treadmill. Pre-and post-flight test protocols have been performed by crewmembers since Expedition 5; these crewmembers will serve as controls.

Test of Midodrine as a Countermeasure Against Post-flight Orthostatic Hypotension (Midodrine, J. Meck, NASA Johnson Space Center, Houston, TX). Approximately 20% of short duration and 80% of long duration crews experience orthostatic intolerance immediately post-flight. Previous research, including a bed rest analog study, demonstrated efficacy of Midodrine, a clinically approved medication (approved by the U.S. Food and Drug Administration), for orthostatic intolerance. Interactions with other pharmaceuticals were also determined and flight rules have been written to assure safe use of Midodrine. The efficacy of Midodrine for long-duration astronauts was first tested when taken after landing on Expedition 5. During Expeditions 11 - 13, Midodrine will be taken orally by Space Shuttle (short duration) crewmembers approximately one hour before re-entry/landing. Efficacy will be determined by use of a standard cardiovascular tilt table protocol. Testing of this countermeasure on short-duration crewmembers will allow a suitable sample size to be obtained rapidly. This will minimize the number of ISS long-duration test subjects needed.

Bioavailability and Performance Effects of Promethazine During Spaceflight (PMZ, D. Harm, NASA Johnson Space Center, Houston, TX). Many crewmembers experience nausea (space motion sickness, SMS) when they transition from gravity to weightlessness. Promethazine (PMZ) is the anti-motion sickness drug of choice at NASA, however, virtually nothing is known about the bioavailability and performance effects of this drug in the microgravity environment. Anecdotally, it appears that the side effects of fatigue and decreased alertness observed when this medication is taken on Earth are reduced when it is taken in space. Focusing on Space Shuttle crewmembers on their way to ISS, this experiment will establish the bioavailability and performance effects of intramuscular PMZ during flight and examine the impact of space motion sickness and fatigue on crew performance. Salivary and urinary PMZ concentrations and their pharmacokinetic variables will be correlated with objective measures of performance/impairment. Establishing the correct dosing and understanding the side effects of this countermeasure for SMS is important for ensuring optimum performance of exploration crews. Similar reactions often also occur upon reentry to Earth's gravitational fields and landing, and might occur when leaving the Moon for transit back to Earth, at landing on Mars, and when leaving Mars for transit back to Earth.

2.3 Physiology in Microgravity: Immune Function

Although the few clinical events of infection observed in space cannot be directly attributable to declining immune function, there are strong indications that immune performance declines during stays in space [27, 28]. Changes in immunity may be due to presence of stress hormones released before and during flight [29], decreased immune stimulation within a pristine environment, and intrinsic effects of microgravity and/or radiation on immune function. Concurrently, physiological conditions consequential to adaptation to space may favor activation

of latent viruses or affect the virulence of otherwise innocuous human microbial flora. Better understanding of the linkage between declining immune performance, virus reactivation, and changes in microbial virulence can be obtained from ISS studies, and allow better assessment of these risks to future exploration missions. Two studies of viral reactivation are currently in progress on ISS.

Space Flight Induced Reactivation of Latent Epstein-Barr Virus (Epstein-Barr, Raymond Stowe, Ph.D., The University of Texas Medical Branch at Galveston, Galveston, TX). Most adults in the U.S. have been infected with Epstein-Barr virus (EBV), which establishes a lifelong dormant infection inside the body that can be reactivated by illness or stress. The work is being extended to long duration crewmembers. Investigators will analyze stress hormones and cytokines (immune system indicators), EBV replication, and virus-specific T-cell immune function. The first study participants were crewmembers during Expeditions 5 and 6, and more subjects will participate in Expedition 11 and beyond. A total of 18 long-duration and up to 62 short-duration (Shuttle crew) subjects are being sought, with 3 and 17 subjects completed to date, respectively.

Reactivation of additional viruses is also continuing to be studied in Space Shuttle astronauts on ISS construction missions as part of *Latent Virus* (D. L. Pierson, NASA Johnson Space Center, Houston, TX) begun during Expedition 5, with 40 of the targeted 60 subjects complete. Preliminary results have indicated reactivation of Epstein-Barr virus [30], Varicella zoster virus [31], and Cytomegalovirus [32] in short-duration (Space Shuttle) crewmembers.

These studies will provide indirect information on the extent of decreased immune function observed when crewmembers are in microgravity, as well as specific information on the potential threats of reactivated viruses to the health of crews on future long-duration missions. Also relevant to the integrated picture of immune function and risk to human exploration, a study of the microbial environment is discussed in Section 2.7, *Yeast-Group Activation Packs (Yeast-GAP, C. A. Nickerson, Tulane University, New Orleans, LA)* grew yeast cells during Expedition 8 to determine differences in gene expression in orbit; additional studies of microbial growth are also planned for ISS in the near future. These studies would validate observed changes in microbial virulence in space analogs [e.g., 33].

2.4 Human Behavior

Human behavior on long-duration missions is an area well-studied in ground analog situations (e.g., Antarctic research posts). Long duration space missions include, by their very nature, many pressures on group and individuals that could compromise mission success. NASA has initiated studies to better understand these dynamics.

Crewmember and Crew-Ground Interaction During International Space Station Missions (Interactions, Nick A. Kanas, Veterans' Affairs Medical Center/University of California-San Francisco, San Francisco, CA). Completed during Expeditions 2-9, this experiment measured the impact of cultural and language background on space missions and evaluated changes over time in interpersonal factors such as tension, cohesion, leadership roles, and the relationship between space crews and monitoring personnel on Earth. ISS crewmembers and mission control personnel responded to questions from three standard mood and interpersonal group climate questionnaires and maintained critical incident logs. Previous studies of crew interactions when U.S. crewmembers were added to *Mir* crews, identified important patterns of responses in interactions between and among crews and ground personnel (e.g., [34,35]), and many of the behavioral factors studied in this experiment (communication styles, multicultural teams,

operational systems) will be important in planning operations systems and relationships between exploration crews and ground personnel for lunar and Mars missions. In contrast to studies of isolated explorers in the Antarctic, preliminary results of this study indicate no change in well-being during the third-quarter or second-half of a mission [36]. Unlike U.S. crewmembers on *Mir*, there was no evidence of displacement of negative feelings to outside supervisors [36]. Not surprisingly, the investigation is also identifying differences in mood and group perceptions between Americans and Russians and between crewmembers and mission control personnel. International Space Station (ISS) crewmembers show evidence of improvement in mental health as they adjust to the environment (adaptation), and post-mission surveys of crewmembers are being used to evaluate strategies to enhance crewmembers' in-flight stress tolerance and post-flight adjustment [37].

Behavioral Issues Associated with Long Duration Space Expeditions. Review and Analysis of Astronaut Journals (Journals, J. Stuster, Anacapa Sciences, Inc., Santa Barbara, CA). The premise for this study is that introspective accounts of individuals operating under isolated and confined conditions can provide useful information about the factors that affect individual and group performance. Previous work investigating isolated and dangerous expeditions on Earth yielded quantitative data that were used to develop a rank-ordering of behavioral issues in terms of salience or importance. The objective of this present study is to obtain behavioral and human factors relevant to the design of equipment and procedures to support adjustment and sustained human performance during long duration isolation and confinement. Participants make journal entries at least three times weekly using a personal journal or a laptop computer. The experiment has been ongoing since Expedition 8 and is planned for completion by Expedition 13.

2.5 Clinical Medicine

As part of the Crew Health Care System (CHeCS), the ISS houses a suite of clinical medical equipment including elements to help prevent, diagnose and treat medical problems that might arise during a mission [38]. The health maintenance subsystem is limited in scope due to mass, volume, and technology constraints, but includes an ambulatory medical pack, advanced life support pack, crew medical restraint system, defibrillator, respiratory support pack, and crew contamination protection kit (see discussion of clinical care on ISS in [39]). Research to improve clinical medicine as practiced in space has been targeted at improving diagnostic technologies and providing better monitoring of crew health. Early investigations have included a study of pulmonary function after spacewalks (*PuFF*), and a study evaluating extension of diagnostic ultrasound beyond the standard uses on Earth (*ADUM*) to improve remote diagnostic capabilities.

Effects of EVA and Long-Term Exposure to Microgravity on Pulmonary Function (PuFF, John B. West and Kim Prisk, University of California, San Diego). Completed on Expeditions 3-6, this study examined the effect of long-term spaceflight and Extravehicular Activities (EVAs, i.e., spacewalks) on pulmonary function. Over a long-term flight, there is possible exposure to noxious gases or particulate matter in the closed atmosphere of the ISS. EVAs, like reverse-pressure deep water dives, involve significant changes in pressure and composition of air breathed by the astronauts, which could impact lung function. To examine these effects, long duration crewmembers conducted a battery of non-invasive tests of pulmonary function to assess whether changes occur over the course of a stay on ISS with multiple EVAs [40]. Because of mission requirements, data collections immediately following EVAs were not possible, so it remains unknown whether there are significant pulmonary function changes immediately post-

EVA. The data do suggest, however, that the denitrogenation (i.e., prebreathing) protocols currently in use on ISS result in no lasting adverse effects on lung function [41]. Validation of these protocols is important as design decisions are made for future spacesuits—including atmospheric composition, pressure, and protocols for EVA activities that will be carried out on the moon and Mars.

Advanced Diagnostic Ultrasound in Microgravity (ADUM, Scott A. Dulchavsky, Henry Ford Health System). ADUM established norms for imaging of organs and tissues in microgravity and also evaluated the ability of crewmembers to perform ultrasound imaging that might be required (as in the case of an injury) using the shoulder and abdomen as examples [42,43]. Crews received 2.5 hours of ultrasound training several months before the mission and a 1-hour review on orbit, but no specific training in detailed anatomy or ultrasound techniques (sonography programs typically require 1-4 years of study) [44]. The real-time ultrasound images were transmitted to remote experts on Earth who verbally guided the astronaut performing the sonography. New data on ultrasound imaging of organs and systems in microgravity becomes an important foundation for ultrasound diagnostics now and in future exploration missions. The demonstration of focused assessment with sonography for trauma (FAST) shows the flexibility in using ultrasound in space to improve remote medical capabilities for long-duration missions to the Moon and Mars [43].

In addition to these formal studies, a variety of clinical data is collected on astronauts as part of routine medical monitoring. A variety of hypotheses can be tested and information gained from this additional research. For, example, a recent analysis of food consumption combined with routine monitoring data on body composition, hematology, and blood analysis revealed significant decreases in dietary intake on orbit [45]. Iron metabolism changed during flight, and there were indicators of increased oxidative damage. The analysis focused nutritional concerns for long-duration spaceflight on bone loss, compromised vitamin D status, and oxidative damage [45].

2.6 Radiation

Cosmic radiation is a major risk factor in manned space missions as noted in the *Bioastronautics Roadmap* [4]. Potential synergistic influences such as microgravity, acceleration, vibration, hyperthermia, noise, microwave radiation, physical exercise, trauma, and infections cannot be ruled out with current knowledge. The space radiation field includes a mix of electrons, protons, energetic heavy ions (HZE), and secondary radiation such as bremsstrahlung¹ and secondary neutrons [46]. Radiation exposure depends upon several variables including altitude and inclination of the spacecraft, shielding material and thickness, and solar activity patterns.

The radiation environment on ISS, within the Earth's geomagnetic field, differs significantly from the radiation environment that astronauts will experience on the Moon, in transit to Mars, or on the surface of Mars. With the combination of operational radiation monitoring and research dosimetry, the radiation environment of the ISS has now been characterized. Importantly, hardware and measurement techniques for characterizing the radiation field in Low Earth Orbit can have significant application for exploration missions.

Bonner Ball Neutron Detector (BBND, Tateo Goka, Japan Aerospace Exploration Agency, Tokyo, Japan). High energy secondary neutrons are produced by the interactions of high energy

¹ High-energy electromagnetic radiation released as the primary radiation particles interact with the nuclei of spacecraft shielding materials or the human body and decelerate

charged particles with spacecraft materials and planetary surfaces. *BBND* characterized the neutron radiation on ISS during Expeditions 2 and 3 and determined that galactic cosmic rays were the major cause of secondary neutrons measured inside ISS [47]. The average dose-equivalent rate¹ observed through the investigation was 3.9 micro Sv/hour, with the highest rate at 96 micro Sv/hour, which occurred in the South Atlantic Anomaly region [47]. Although this experiment did not characterize the neutron radiation environment outside of the Earth's magnetic field, the *BBND* sampling equipment provided results without return of equipment to Earth and proved that similar measurement systems could be used on missions to the Moon and Mars to monitor real time radiation risks.

Three experiments have focused on ISS dosimetry, measuring the radiation dose received on ISS. Completed during Expedition 2, *Organ Dose Measurement Using the Phantom Torso (Phantom Torso*, Gautam D. Badhwar, NASA Johnson Space Center, Houston, TX) used a synthetic human torso, embedded with over 500 strategically placed passive dosimeter capsules (containing thermoluminescent detectors) and five Si diode detectors, to determine the absorbed dose and dose equivalent to specific organs in the human body during spaceflight. Concurrent measurements were made external to the phantom with a tissue equivalent proportional counter. This data may help benchmark radiation transport calculations when coupled with the organ-specific measurements.

A Study of Radiation Doses Experienced by Astronauts in EVA (EVARM, Ian Thomson, Thomson & Nielsen Electronics, Ontario, Canada) characterized the radiation doses received by different parts of an astronaut's body (e.g., skin, eyes, and blood-forming organs) during EVA for Expeditions 4-6. Also on Expedition 2, *Dosimetric Mapping (DOSMAP*, Guenther Reitz, Ph.D., DLR Institute for Aerospace Medicine, Cologne, Germany) used four different types of dosimeters in different configurations to map the radiation levels (absorbed dose, neutron dose equivalent, heavy ion fluence, and spectral composition with respect to charge, energy and linear energy transfer) throughout the Station and in the immediate vicinity of each crewmember. Organ doses measured from the Phantom Torso experiment are being combined with results from experiments on the Space Shuttle and previous missions to validate NASA's organ dose database for astronauts. Preliminary results suggest that organ dose and dose equivalent can be projected to a $\pm 25\%$ accuracy using a combination of dosimetry and radiation transport models [48]. This accuracy envelope is greatly improved relative to the current accuracy of organ specific cancer risk projections, estimate at $\pm 500\%$ [48]. Further analyses and incorporation of radiation results into operational planning for exploration is ongoing.

Chromosomal Aberrations in Blood Lymphocytes of Astronauts (Chromosome, G. Obe, University of Essen, Germany). While earlier radiation studies focused on characterization of the radiation environment in low Earth orbit, this on-going study targets cytogenetic effects of exposure. This study will assess whether the ionizing radiation that ISS crewmembers are exposed to while in orbit causes potentially damaging structural changes in specific chromosomes. Ongoing since Expedition 6, three different staining procedures are employed to document and score chromosomal aberrations (classic Giemsa block-staining to score dicentric and ring chromosomes; multi-color fluorescence in situ hybridization [FISH] to score reciprocal translocations and insertions; and multi-color banding FISH of a selected chromosome pair to

¹ In general, radiation damage to the human body is indicated by dose-equivalent amount absorbed in living tissue and measured in Sieverts (Sv). An average background radiation dose received on Earth can be approximately 1000 micro Sv/year without causing serious harm, while an exposure of 1 Sv/hour can result in radiation poisoning. Three to five Sv/hour results in death in 50% of the cases.

score for inversions and translocations between homologous chromosomes). The research is important because chromosomal aberrations are linked with increased cancer risk. Prior work of Obe [49] demonstrated elevated frequencies of dicentric chromosomes in 18 astronauts who stayed in space for more than 100 days. It is anticipated that results from this investigation will lead to a better understanding of the genetic risk to humans exposed to long duration spaceflights.

2.7 Advanced Environmental Monitoring and Control

ISS is envisioned as a test bed to evolve environmental monitoring and control for exploration missions. The first experiment in this area has begun, in the critical area of fire detection and suppression. The second, in the area environmental microbiology, will commence soon.

Requirements defined for smoke detectors in spacecraft have varied significantly, because little is known about the distribution of particles (soot) from fires in space (in the absence of gravity). Soot particles range from 0.1 to several microns, and controlled combustion studies suggest soot particles will be larger in microgravity than burning the same materials on Earth. The *Dust and Aerosol Measurement Feasibility Test (DAFT)*, David Urban, NASA Glenn Research Center, Cleveland, OH) is the first step toward the next generation of smoke detection systems for future exploration vehicles. Preliminary results based on two DAFT sessions performed on ISS in 2005 [50], indicate very low levels of particulate in the ISS environment due to the current small crew and the HEPA filtration system of ISS. Upcoming runs of the experiment will use known dust sources to confirm that the equipment is functioning accurately on orbit. Sampling will also be done at more locations throughout ISS to draw definitive conclusions. This experiment will provide the first systematic measurements of the sizes of particles in the air in ISS over time and prove the usefulness of the P-Trak® Ultrafine Particle Counter in a microgravity environment. If successful, the detector will be used in the *Smoke and Aerosol Measuring Experiment (SAME)*, which will collect measurements of the smoke particulate size distribution on-orbit, and enable the next generation of smoke detectors to be designed to detect the optimal range of particle sizes [51].

During long-duration spaceflight, spacecraft build up a diverse array of microorganisms that directly interacts with the crew of the vehicle. Most microorganisms are harmless or even beneficial to the crew; however, the presence of medically significant organisms appearing in this environment could adversely affect crew health and performance during long duration missions. Previous studies from the *Mir* space station have suggested that microbial contamination will increase as the time the station has been occupied increases [52,53]. Microbes from air, water, and surfaces of the ISS are being monitored to determine a baseline from which future microbial analyses can be compared [54].

A Comprehensive Characterization of Microorganisms and Allergens in Spacecraft Environment (Swab), D. L. Pierson, NASA Johnson Space Center, Houston, TX) begins on Expedition 11. The primary goal of the *Swab* experiment is to use advanced technologies to identify microorganisms, allergens, and microbial toxins present on ISS, and detect patterns of change in the environment. It will go beyond the culture techniques traditionally used to monitor microbes on *Mir*, Space Shuttle and ISS. Understanding the environmental microbiology of spacecraft is important for planning Mars missions, where crews will depend on a closed environment for a long period of time.

2.8 Materials Survivability, Inspection, and Repair in the Space Environment

The space environment poses many hazards to the exposed surfaces of spacecraft, including intense ultra-violet radiation, corrosive attacks from atomic oxygen, radical temperature swings, and strikes from micro-meteoroids and orbital debris. NASA studies of the exposure of materials to the space environment for long periods of time have taken advantage of *Mir* and then ISS as a location to place, mount, and then retrieve sets of test materials. The *Materials International Space Station Experiment (MISSE)*, William H. Kinard, et al., NASA Langley Research Center) has two Passive Experiment Carriers (PECs) with approximately 900 specimens that were mounted outside the ISS airlock in August 2001 (MISSE 1 and 2) and returned by (STS-114/LF1) in August 2005. STS-114 also brought a new PEC to be mounted on ISS (MISSE 5). Two more PECs (MISSE 3 and 4) will be brought up by Shuttle flight STS-121/ULF1.1, and two additional PECs (MISSE 6 and 7) are planned to be brought to ISS on a subsequent Shuttle flight. Analyses of exposed sample survivability will commence upon return of samples.

Soldering conducted in a microgravity environment produces weaker joints than when the same materials are soldered on Earth [55]. The *In Space Soldering Investigation (ISSI)*, Richard Grugel, NASA Marshall Space Flight Center) includes a series of test cases using soldering materials on orbit. Soldering was carried out on Expeditions 9 and 10, with samples to be returned when the Space Shuttle returns to flight. Review of the experiment videotapes revealed melting kinetics, wetting characteristics, and equilibrium shape attainment of the solder charge. Additionally, the accumulated liquid flux was observed to rapidly and circumferentially translate over the surface of the molten solder ball, an unexpected phenomenon that is currently being assessed. Evaluation of the experimental results is expected to promote our knowledge of fabrication and repair techniques that might be employed during extended space exploration missions.

New technologies are also being developed to improve the ability to inspect spacecraft while they are on orbit. *MEMS-Based PICOSAT Inspector (MEPSI)*, J. Keeney, Kirtland Air Force Base, Albuquerque, NM) is a series of tests in the development of tiny (1 kg, 4"×4"×5") autonomous satellites that can be used to observe larger spacecraft. The deployment of the pico-satellites was tested during Space Shuttle flight STS-113. On future Shuttle flights to ISS, a new system will be tested with gyros for stabilization and onboard cameras for making inspections. This technology could be the basis for autonomous inspection capabilities for future exploration vehicles.

3. Future Exploration Research: Reducing the Risks to Explorers

NASA has adopted a risk reduction approach to identify and prioritize major risks to human health due to spaceflight. Some of these risks become more extreme as missions lengthen, others do not. Some can be addressed most efficiently with ground analogs (e.g., bed rest studies); others require testing in space. Most that are of greatest concern for exploration missions will require the ISS, since it is the only platform to conduct long duration testing on humans in space. This section addresses our current understanding of the major exploration mission risks that the ISS can be used to address.

Initially developed as documentation of key research questions in bioastronautics, the *Bioastronautics Roadmap* [4] has evolved as the basis for the identification and reduction of risks of exploration missions to human health. It provides structure for a systematic approach to prevent, control, eliminate or reduce the known risks to crew health, safety and performance during and after long-duration human spaceflight.

In summary, the stated objectives of the *Bioastronautics Roadmap* [4] are to:

- Identify and assess risks for human space exploration missions
- Prioritize research and technology, and communicate those priorities
- Guide solicitation, selection and development of NASA research and technology (both ground-based and flight) and allocation of resources for development of exploration mission deliverables
- Assess progress toward reduction and management of risks through appropriate development of deliverables and products
- Deliver the appropriate products and knowledge necessary to develop: standards; requirements; clinical tools and capabilities for diagnosis and treatment of illness and injury; inputs to mission, task and vehicle design; countermeasures; training and in-flight medical protocols; specific technologies; and components and systems with increased efficiencies.

Using the Roadmap to focus research and technology development strategies will allow reduction of risk through effective and efficient mitigation. As risks are assessed in the context of the Roadmap, program managers can evaluate the expected reduction of a specific risk that can result from an investment in research.

Five overarching issues that are important for defining and reducing human health risks of future exploration spaceflight are:

- Ground-based integrated testing involving both humans and spacecraft systems is required in such areas as environmental life support testing, countermeasure evaluation and validation, and end-to-end testing to assure readiness for flight tests.
- Risks addressed must be based upon operational issues, not hypothetical or research-based. A number of theoretical risks have been posed from basic physiology or inferred from studies of short-duration missions. Whenever possible, existing operational data from long-duration missions to ISS, *Mir*, or Skylab should be used to validate these potential risks of spaceflight and make preliminary quantitative risk assessments. Research effort needs to be expended on the most important risks, and there is not time to completely address every possible risk to human health before sending crewmembers beyond Earth orbit.

- Key drivers for human system requirements must be incorporated into spacecraft and mission designs early in the process. For example, radiation shielding of spacecraft habitable volume and refuge areas can be a significant design element for materials and mass, and has significant effect on the human health risks of acute and chronic radiation exposure. Similarly, habitability standards that impact human health—from acoustics to lighting to usability—are closely tied to early mission designs.
- All support hardware for human performance maintenance must be designed with high reliability. A major lesson learned from ISS to date has related to reliability across such disparate areas as exercise equipment failures (discussed in Annex 1), to the need for more environmental control and life support systems (ECLSS, [5]) that are independent from the need for resupply from the ground. Exploration missions will not have the option of rapid medical evacuation to Earth, making reliable diagnostic and therapeutic equipment extremely important,
- An integrated approach is required to develop efficient engineering solutions for the human support systems that avoid excessive resource costs. Human support systems must have minimal mass and power consumption, low consumable requirements, high reliability, and low maintenance.

How should ISS be utilized as a research platform to address this myriad of requirements? First we should consider those areas requiring the unique environment of space. Specifically, we should focus on countermeasure verification which typically requires the space environment to be certain the countermeasure is effective. Bone loss countermeasures must be verified in flight whether they involve specific exercise protocols, pharmaceutical approaches, or a combination. The next generation of exercise equipment needs to be tested on ISS, with improved reliability, improved comfort so that crewmembers can achieve suitable ground-reaction forces for maintaining bone and muscle, and possibly with accompanying visual stimuli to improve locomotor responses to changes in gravity. Cardiovascular research is necessary to determine if significant heart mass or function is lost and if important arrhythmias occur during long duration missions. Behavioral health and performance studies are necessary to determine how to optimally support long duration crews and maintain their proficiency where studies of analog environments (e.g., Antarctic outpost studies) are insufficient. Radiation exposure is a significant issue for exploration of the Moon and Mars, however, it can best be studied using controlled radiation exposures of animal and cell culture models in ground studies [56]. Finally, ISS should be utilized as a test bed to evaluate technologies such as advanced environmental control systems and monitoring equipment, as well as material survivability, inspection and repair.

Because much of this work involves the study of human biological systems, it must be carried out using statistically significant sample sizes in order to draw appropriate conclusions. The available population for study on the ISS is extremely limited. As noted earlier, 28 astronauts and cosmonauts have served on long-duration Expeditions aboard the ISS in the 4 years it has been occupied. Critical factors determining the numbers of human subjects available are the number of ISS crew members in residence, and the duration of each Expedition. The shift back to a crew of three (when the Space Shuttle returns to flight) and the potential for larger crew complements are important factors for obtaining sufficient numbers of human subjects. Expedition duration is also an important factor. The nominal Expedition of 120-days is the optimal length for most human life science experiments; allowing sufficient time for long-duration effects to manifest and stabilize into predictable patterns. Expeditions of 120 days

allow more astronauts to cycle through the ISS, and thus increase the sample size for human research experiments. The increase in numbers carries a resulting increase in logistical overhead for the ISS program that must be carefully managed. Nonetheless, Expeditions of 120 days have been recommended by all of the advisory organizations overseeing ISS research. Strategic planning in progress will also focus the set of research questions and approaches and optimize the numbers of human subjects needed on ISS.

4 Conclusions

The objectives for research on ISS have recently shifted from a broad-based pursuit of fundamental and applied research questions to a targeted effort to reduce risks for NASA's exploration missions. Nonetheless, the first four years of long-duration space research on ISS have provided answers or insight into the following issues that are highly relevant to NASA's exploration missions:

- Differentiation of bone loss (i.e. where it occurs and how much is lost)
- Detailed understanding of muscle mass loss
- Direct observation of muscle fiber changes
- Characterization of loading on legs and feet during exercise
- Test of drug efficacy in prevention of renal stones
- Observation of the veno-arteriolar reflex (reflex that prevents blood from pooling in legs in 1-g) that appears to function normally in space.
- Test of mitigation for post-flight locomotor dysfunction
- Testing of a pharmacological countermeasure for post-flight orthostatic intolerance
- Understanding of space motion sickness drug uptake
- Understanding of relationship dynamics between crews in space and ground control team
- Examination of factors that affect individual and group performance
- Pulmonary function assessments showing no adverse pulmonary effects from EVA pre-breathe protocols
- Use of ultrasound as remote diagnostic tool and for imaging physiological changes (e.g., organ shift) over time
- Full Characterization of the ISS Radiation environment
- Characterization of radiation dose to specific organs
- Characterization of radiation doses during extra-vehicular activities
- Characterization of some genetic effects of radiation exposure
- Characterization of immune function changes in spaceflight
- Characterization of medically significant microorganisms and allergens on ISS
- Refinements to smoke detection design
- Testing of material response to the space environment
- Development of methods for in-space inspection, fabrication and repair

Future research on ISS is being targeted towards areas such as advanced environmental control and monitoring, human health and countermeasures, advanced life support systems, and development of better medical care and exercise equipment.

The fundamental challenge for research on ISS is completing experiments that answer key questions in time to shape design decisions for future exploration. In this context, exploration-relevant research must do more than be conceptually connected to design decisions—it must become a part of the mission design process.

Annex 1: ISS Operational Exercise Hardware & Exercise Prescription Evaluations

The ISS houses a resistive exercise device, a cycle ergometer, and a treadmill. Each crew member maintains an exercise prescription, and is allotted time during the work day to do so. Exercise equipment used on ISS is pictured in Figure 1.

ISS exercise prescriptions cannot be evaluated critically at this time because of poor hardware reliability and inadequate instrumentation necessary to quantify exercise sessions. Statistical evaluations are not yet meaningful due to the limited crew subjects. However, it is known that the loading available on the equipment is probably inadequate, relative to body mass loading available in 1-g. This is borne out in the *Foot* experiment data [22], where peak forces experienced during treadmill runs were approximately 63% of the forces that would have been experienced running on a treadmill on Earth.

The interim resistive exercise device (iRED) has been unreliable. Total available force is limited to 136 kg (300 lbs) compared to the required 272 kg (600 lbs). The force packs have recently been replaced with the upgrade referred to as the SchRED (Schwinn Resistive Exercise Device). Efficacy of the SchRED will be determined within the next 36 months. A full replacement device is presently being evaluated in the laboratory. This Advanced Resistance Exercise Device (ARED) is based upon a different force system and should provide designed loads up to 272 kg (600 lbs). The challenge for the ARED is to provide much greater loading capability while constraining volume and mass to an acceptable level for flight hardware.

The cycle ergometer with vibration isolation (CEVIS) has performed well with minimal maintenance. It is compact and suitable for exploration class missions.

The treadmill with vibration isolation (TVIS) needs substantial improvement. The ISS unit has a significant limitation in belt speed and inadequate force measurements and reliability in the subject load device (SLD). Furthermore, if settings on the SLD were chosen to provide force equivalent to what would be experienced running on Earth [22], the equipment is extremely uncomfortable. For exercise on future long duration missions, it would be highly desirable to evaluate a split tread design with virtual reality display; these enhancements would provide better exercise capability combined with reduced subject boredom. Ideally the equipment will also measure forces so that exercise effectiveness can be more readily monitored during a mission.

The current exercise technologies used in space are not sufficient to support crew health on a mission to Mars. Given the needed improvements, reliability problems in current technology, and that fact that exercise equipment mass will likely need to be reduced for a Mars mission, we clearly need to fly and test the next generation of devices prior to Mars mission. ISS provides an important opportunity for long duration testing of the next generation of exercise technology, and for validation of the role of exercise combined with other countermeasures in protecting against bone and muscle loss.

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13. ABSTRACT (Maximum 200 words) In January, 2004, the U.S. President announced The Vision for Space Exploration, and charged NASA with using the International Space Station (ISS) for research and technology targeted at supporting U.S. space exploration goals. This paper describes what we have learned from the first 4 years of research on ISS relative to the exploration mission, the on-going research being conducted in this regard, and our current understanding of the major exploration mission risks that the ISS can be used to address. Specifically, we discuss research carried out on the ISS to determine the mechanisms by which human health is affected on long-duration missions, and to develop countermeasures to protect humans from the space environment. These bioastronautics experiments are key enablers of future long duration human exploration missions. We also discuss how targeted technological developments can enable mission design trade studies. We discuss the relationship between the ultimate number of human test subjects available on the ISS to the quality and quantity of scientific insight that can be used to reduce health risks to future explorers. We discuss the results of NASA's efforts over the past year to realign the ISS research programs to support a product-driven portfolio that is directed toward reducing the major risks of exploration missions. The fundamental challenge to science on ISS is completing experiments that answer key questions in time to shape design decisions for future exploration. In this context, exploration-relevant research must do more than be conceptually connected to design decisions- it must become a part of the mission design process.				
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