Sustainability of Microgravity R&D During and Beyond ISS Transition

RESPONSE TO THE REQUEST FOR INFORMATION FROM THE U.S. OFFICE OF SCIENCE AND TECHNOLOGY POLICY (OSTP) – 87 FR 69059 DOCUMENT NUMBER 2022-24999

30 December 2022

Elizabeth Heider, PhD | Cap-Geo
Christopher Puhl, PhD

Sustainability of Microgravity R&D During and Beyond ISS Transition; response to RFI from the OSTP*

Elizabeth Heider† & Christopher Puhl‡

WHAT SHOULD BE THE UNITED STATES' VISION FOR THE FUTURE OF MICROGRAVITY RESEARCH?

The International Space Station (ISS) is a multifaceted entity. It's a symbol of international collaboration, it signals our intention for peaceful (non-military) endeavors in space, it encourages young people to pursue careers in STEM fields, and inspires the creation of art and media. It also serves as a test-bed for developing ideas and technologies, spurring innovation, commercial development, and economic growth, while enhancing our understanding and shaping the requirements for future space exploration missions. Finally, it's a unique research platform for probing the fundamental laws of nature, producing profound and unexpected understanding of fundamental physics (e.g. material science, combustion, and fluid dynamics), and terrestrial biological processes, including valuable insights into human physiology.

As the ISS counts down to retirement in 2030, it's easy to believe that the goals of the program will not be lost since its most visible attributes will be retained in Lunar and Mars missions. Such missions will no doubt serve as powerful symbols of collaboration and inspire the next generations. They may also drive engineering innovations and spur growth in the space economy. But it would be a mistake to assume that these features will compensate for the loss of the ISS, since they don't also take into account the role of the ISS as a research platform.

There is no terrestrial replacement for ISS science, meaning that the loss of the station is fundamentally different from any other research facility.[1] Certainly, the planned cis-lunar deep

---

*The White House Office of Science and Technology Policy (OSTP) requests input to help inform the development of a National Strategy for Microgravity Research and Development (R&D) to ensure sustainability of space-based research during and beyond microgravity platform transition—from the International Space Station (ISS) to future commercial platforms. This particular request seeks information regarding the future vision of a robust research ecosystem in low-earth orbit (LEO) and the role of the U.S. government in enabling that future. Document 87 FR 69059. Document Number 2022-24999
https://www.federalregister.gov/documents/2022/11/17/2022-24999/request-for-information-sustainability-of-microgravity-randd-during-and-beyond-iss-transition

† Corresponding author: heidere@cap-geo.com . Dr. Heider is a U.S. Citizen contracted as a scientist for the European Space Agency. Opinions represented in this report are her own and do not reflect those of her employer or the agency. Dr. Heider is also a company owner of the analytical consulting firm CAP-GEO. The opinions and ideas expressed in this report are those of CAP-GEO.

‡ Chrispuhl50@gmail.com. Dr. Puhl is a U.S. citizen contracted as a scientist for the European Space Agency. Opinions represented in this report are his own and do not reflect those of his employer or the agency.

space gateway will not be able to fully replace the ISS R&D program due to the extreme constraints, costs, risks, and technical challenges of conducting research at such a distance.

The ISS already imposes strict limits on the mass and volume of equipment and supplies. Additionally, research payloads are subjected to high inertial forces during takeoff and landing, and are exposed to high doses of ionizing radiation that can damage both hardware and software[2]. These challenging conditions are further complicated by the presence of microgravity, which can alter the intended functioning of equipment[3]. Research on the ISS is also limited by power and heating and ventilation requirements, as well as the types of materials (including safety and toxicity) that can be used. These constraints are further exacerbated by the limited time and labor available to on-board crew, who must divide their research time with basic tasks to maintain their habitat. Research on a cis-Lunar Deep Space Gateway station will face even more extreme challenges, including high transport costs, significant delays in communications and support, restricted chances to replace broken equipment, and reduced opportunities to conduct sensitive biology experiments with fragile living samples that would not survive the added transport time[4]. Crew time will be extremely limited both in terms of the execution of individual experiments and mission duration. Importantly, the shorter mission lengths of cis-lunar missions will not allow for the study of important aspects of human physiology that can only be achieved with long-duration (6 months or more) missions.

Other concerns arise when considering the use of a commercially-driven agenda for research in Low Earth Orbit (LEO) through the creation and direction of a commercial LEO station. While such a platform may provide some research opportunities, it is likely to focus on areas that are most profitable, potentially excluding important academic research questions whose application may not be immediately obvious. It will be important, therefore, for the U.S. to develop and fund a rigorous microgravity research agenda.

In forming its agenda, the U.S. vision should focus on a deeper exploration into the key discoveries we've made aboard the ISS, particularly in biological systems and human health. To do this, human physiology and biology research should play a central role. Concurrently, we should also make significant investments to facilitate and develop those technologies that have the potential to drastically impact terrestrial human health outcomes such as 3D bioprinting with the goal of 3D bioprinting functional human hearts within the next decade. Next, the goal should be to use *in vivo* research to carry out integrative studies that incorporate genetic, cellular, and behavioral responses to space stressors, including microgravity, radiation, and isolation, to provide a more comprehensive understanding of how the space environment affects human health and identify potential interventions to mitigate negative effects. Finally, the goal should be to study the effects of the space environment on materials and structures, and developing new technologies and capabilities that can benefit both space exploration and life on Earth. We discuss each of these research goals in more detail in the section below. In addition to providing direct benefits and applications on Earth, this LEO research will set the boundaries and produce the technologies needed for safe and sustainable long-term deep space presence.

WHAT SHOULD BE THE LONG-TERM MICROGRAVITY RESEARCH GOALS FOR U.S. PRESENCE IN LEO?

1. **The U.S. government's primary microgravity research priority should be understanding human health, using the microgravity environment to reveal fundamental biological functions, and leveraging the analogs for human disease.**

   Space offers a crucial platform for studying changes in the human body. The unique stressors of the LEO environment can initiate genetic adaptations and alter cellular processes, mimicking various terrestrial maladies in otherwise healthy subjects. This allows researchers to probe the underlying mechanisms of disease and aging, and can provide valuable insight into analogous conditions on Earth. For example, researchers have used the LEO environment to study alterations to the immune system[5], circadian rhythm[6], temperature regulation, the microbiome, the cardiovascular system[7], the eyes, skin, and epigenetic gene expression to name a few[8]. Additionally, research using ISS crewmembers has been the only model of sufficient length to investigate the effects of unloading and immobilization on physiological mechanisms such as bone[9] and cartilage adaptation[10] , which have very slow response rates and require long-term study to observe tissue-level changes. Furthermore, neurological adaptations to the microgravity environment are also giving researchers novel insights into the brain. Pre- and post-flight MRI brain scans of astronauts and cosmonauts revealed a number of changes in brain structure and function in response to space conditions – such as reductions in brain volume and changes in the distribution of brain tissue[11], and even the growth of new brain cells in the motor centers of the brain.[12] Complementary neurological studies[13] show alterations in brain functioning, performance, and sensory perception, giving valuable insights into how the central nervous system gathers and integrates perceptual information, mechanisms that have real and immediate application for brain diseases on Earth (such as Parkinson's disease, multiple sclerosis, and traumatic brain injury). Lessons learned from these studies[14] have been applied to develop ability-assist tools for disabled persons, and to improve the functioning of haptic telerobotic systems - such as those robots used in surgeries. Despite the strides made in human physiology research in microgravity, the research represents only a fraction of the first steps needed in the field – work that should not be prematurely cut short with the end of the ISS. Twenty-two years of ISS research seems like sufficient time to discover the impact of the space environment on the human body, but the duration of the average crew mission in this environment is relatively small (6 months or less) and the number of humans to spend time aboard the ISS is fewer than 300 (As of May 2022, 258 individuals in total). In terms of human research trials, this sample size is hardly enough to scratch the surface, especially when you consider that most ISS human physiology research projects have fewer than ten subjects. Future missions should include health data collection from all astronauts (commercial and institutional) as well as the prospect of longer-term (greater than 1 year) missions.

   We note here that there are rigorous processes to protect human research subjects aboard the the ISS established by the Code of Conduct for the International Space Station

Crew,[15] and maintained by the Human Research Multilateral Review Board (HRMRB). It will be important to ensure that similar processes and protections are in place for human subjects aboard all future microgravity platforms.

2. **The U.S. should prioritize the development, growth, and use of 3D bioprinting in space with the ultimate goal of 3D bioprinting functional human hearts within the next decade.**

3D bioprinting is a process that involves using a 3D printer to fabricate living tissue or organs from cells and other biomaterials.[16] This field, while relatively nascent, holds great promise for use in transplants and other medical procedures.[17] Since the first successful bioprinting of functional human tissue in 2006, bioprinting technology has advanced significantly and is being used for a variety of purposes, including the production of tissue and organ prototypes for drug testing, the creation of artificial skin and bone for transplants, and the development of personalized medicine.[18]

One major challenge in 3D bioprinting is the collapse of delicate or complex structures due to their weight. This problem is ameliorated in space since veins and arteries and organs bioprinted in microgravity do not require structural support, allowing delicate tissues to maintain their structure throughout the entire print process.[19] Before sending the bioprints back to Earth, the tissues may then be conditioned using cell culturing systems to further strengthen the tissue for self-support.

The first demonstrations of bioprinting in space have already been conducted aboard the ISS with the support of various space agencies.[20] [21] The success of these experiments has important implications for the future of medicine, as it could potentially lead to the development of a reliable and sustainable supply of tissues and organs for use in transplants and other medical procedures. The market for 3D bioprinting is expected to experience significant growth in the coming years, with some estimates suggesting that it could reach a value of over $4.5 billion by 2024. We anticipate that there will be a significant international development of space-based 3D bioprinting technologies, ultimately heralding a new era of medicine. The U.S. should invest in the necessary resources to maintain its leadership in this promising technology and work towards the goal of 3D bioprinting functional human hearts within the next decade.

There are significant hurdles to overcome if 3D bioprinting is to reach its potential. We note some of them here:

1) Cell survival and viability - that is, ensuring that the cells used in the process survive and remain viable during and after the printing process. This requires the development of specialized biomaterials that can support cell growth and function, as well as the development of printing methods that can accurately deposit cells in the desired locations.

2) Retention of tissue function. While various tissues have been printed that do exhibit many of the functions of their in vivo counterparts, this functionality normally lasts

for approximately 10 days. After this point most printed tissues lose their function. A number of different mechanisms have been proposed to solve this problem, including using extracellular matrix proteins within the printed structure as well as altering the cell cycle dynamics within the tissue itself, but at most these solutions provide marginal extensions for the time the tissues remain functional. For more complex tissues this problem requires significant research investment in order for 3D Bioprinting to become an avenue for bona fide regenerative medicine.

3) Scaling up production to create larger, more complex tissues and organs. This requires the development of larger and more sophisticated bioprinting systems, as well as the development of strategies for integrating multiple tissue types and vascular networks into a single construct.

4) Developing the materials used to print cells and other biomaterials in a way that is biocompatible, able to support cell survival and function, and capable of maintaining their structural integrity during the printing process.

5) Ensuring that the tissues and organs produced through this process are compatible with the body and can integrate with the body's existing tissues and systems.

3. **The U.S. should prioritize the use of in vivo research with the goal of carrying out integrative studies that incorporate genetic, cellular and behavioral responses to space stressors.**

As we transition from carrying out research in LEO to potentially occupying deep space and other planets, a critical question as to the long term effects of these environments needs to be addressed *at all levels*. Questions of this type include: measuring the nature of genetic 'drift' over time in the space environment with links to organ and tissue development as well as cognition; understanding the effect of micro- or partial gravity on the development of the whole organism and the subsequent behavioral consequences; the fidelity of reproduction in microgravity and/or partial gravity.

To answer these questions, we need to carefully select model organisms and the appropriate facilities to house them. Standard models from terrestrial science, such as drosophila (fruit flies), zebrafish, and mice, can be used to leverage genetic tools for further research. These organisms have the advantage of being relatively small and reproducing quickly, which allows for the study of multiple generations born over time in LEO. By studying these organisms through a range of integrative methods, including spaceOMICs, cell culturing (including the potential use of cells for 3D bioprinting), and behavioral assays, we can assess the long-term effects of the space environment on the organisms as a whole. Zebrafish have the added advantage of being transparent, which allows for direct visualization of tissue development as the organism grows.

Taken together over time, these studies could link molecular changes in the genetics of organisms with alterations to function in particular systems and subsequently behavioral changes in the animal model.

This type of integrative research would provide potential targets for countermeasures that could subsequently be tested in orbit. It would also identify biomarkers that may signal the need for medical intervention for crew members. In addition to space-based applications, targets for therapies on earth could be identified as well as fundamental biological principles which would enrich the field as a whole. Moreover *in vivo* integrative systems such as these would complement any 3D Bioprinting research carried out - what better model for organ development than a whole organism? In this way the in vivo research and tissue engineering research can 'talk' to each other and provide mutual benefits.

4. **The U.S. should prioritize materials science research in space**

The ISS material science research has shown prolific outcomes in the past decades. Due to the ongoing, comprehensive, high-throughput nature of these payloads, these experiments are perhaps the most abundant in terms of producing new physical insight, publications, and facilitating further academic research. One example is the Electromagnetic Levitator (EML), a long-running payload hosting the study of many experiments and hundreds of samples. Another is the Material Science Research Rack (MSRR) and the Material Science Laboratory (MSL), providing outstanding scientific and industrial value. The MSL allows the study of microstructure features of materials during the solidification process – such as in casting, welding, soldering and additive manufacturing. The initial cast structure plays a deterministic role in chemical and structural distribution in the material. Material properties are highly dependent on these distributions as well as the microstructure features of the material. If microstructure evolution dynamics under various experimental conditions are known, material properties can be optimized, superior materials - and hence engineering components that will function at extreme conditions - can be designed. Such modeling and optimization relies on the empirical investigation of microstructure evolution during solidification. On Earth, this solidification is affected by convection. Therefore, microgravity solidification studies are needed to reveal the fundamentals of these processes in three-dimensional (3D) samples, and to examine the direct effect of experimental parameters on microstructure selection. Data are used to validate existing models and to provide experimental references. Structural studies of materials are used for a variety of applications that include aerospace components, biomedical implants and surgical tools, sports gear, architecture, and jewelry. The thermophysical property data obtained from the experiments serve as input data for computer models that are used to predict and optimize manufacturing processes (casting) for such components. Other successful material science payloads have included plasma research and diffusion research. These research areas should also be prioritized.

WHAT WOULD BE THE MOST EFFECTIVE ROLE OF THE U.S. GOVERNMENT TO ENSURE SUSTAINED LEO MICROGRAVITY R&D FOLLOWING THE RETIREMENT OF THE ISS?

1. The U.S. Government should establish policies, laws, and processes to address the liability concerns of commercial companies in the context of human exploration in Low Earth Orbit (LEO). These measures would help alleviate the risk of liability for companies participating in such missions, which carry inherent risks and may result in fatalities.
2. A commercial Low Earth Orbit station will necessarily be oriented towards commercial markets. Understandably, this will direct activities to research and development and manufacturing in the areas most likely to produce the highest profit. Initially, this will be oriented towards goods and services for Earth use. As the space economy grows, we should expect to see space-for-space products and services increase. In each instance, applicability and profit will be the drivers. In each scenario, it's unlikely that a rigorous program of academic research would be profitable to make the cut. This could result in missed opportunities for fundamental exploration-enabling research or high costs for NASA/US taxpayers. This could limit the scope and focus of research in the space industry. Therefore, the US Government should establish funding mechanisms and direct research priorities for fundamental space-based research.
3. Currently, telecommunications satellite infrastructure is the dominant part of the LEO economy. There is not currently a market for LEO research, development, and manufacturing for either earth-bound products (space-for-earth), or those which will be used in space (space-for-space), due in part to the high barriers to entry and ignorance of the field. In the future, it is possible that self-sustaining space-for-earth and space-for-space economies may emerge, but this will require active government involvement and funding to support the growth of this market. For the first ten years post-ISS, the government should establish business subsidies and incentives to offset the initial high costs. Government programs should also be put in place to educate and guide space-curious researchers and companies to chart a path to LEO.
4. To incentivize manufacture and space-based resource extraction, the U.S. should establish clear regulations regarding the ownership of products in space.
5. The U.S. should establish clear processes and regulations to protect human research subjects aboard space-based platforms - similar to the Code of Conduct for the International Space Station Crew. We recommend that the federal government also maintain processes and oversight mechanisms to ensure compliance and protection.
6. The U.S. and its partners should establish international standards for payload interfaces and designs that are widely accepted across the entire space industry (similar to the standard shapes of plugs and sockets in homes or USB connectors). This would reduce the proprietary drives of commercial companies, lower costs, and make it easier to develop hardware in some cases.

SHOULD THE U.S. GOVERNMENT CONTINUE TO SPONSOR A NATIONAL LAB IN LEO AFTER ISS TRANSITION? IF SO, WHAT WOULD BE THE BEST MODEL(S) FOR A LEO NATIONAL LAB?

Maintaining a national lab in Low Earth Orbit (LEO) would ensure that the interests of the US in space are represented, rather than solely relying on commercial interests. LEO is an ideal location

for prototyping and testing space technologies for future exploration. When considering the value and type of microgravity research to be funded, facilitated, and grown by the United States, the following criteria should be applied:

- Quality: Research proposals should be thoroughly reviewed for quality and technical feasibility.
- Uniqueness: Research that is unique and cannot be replicated elsewhere should be prioritized.
- Impact: Research that has the potential for significant impact on space exploration or other areas should be considered.

---

[1] P. Castaño, From Value to Valuation: Pragmatist and Hermeneutic Orientations for Assessing Science on the International Space Station, The American Sociologist 52(4) (2021) 671-701.

[2] T. Kuwahara, Y. Tomioka, K. Fukuda, N. Sugimura, Y. Sakamoto, Radiation effect mitigation methods for electronic systems, 2012 IEEE/SICE International Symposium on System Integration (SII), 2012, pp. 307-312.

[3] J.A. Robinson, Research on the International Space Station: understanding future potential from current accomplishments, 58th International Astronautical Congress, Hyderabad, India, 2007, 24-28 September.

[4] F. Ferranti, M. Del Bianco, C. Pacelli, Advantages and Limitations of Current Microgravity Platforms for Space Biology Research Ferranti, Appl. Sci. 11(1) (2021) 68.

[5] B.E. Crucian, A. Choukèr, R.J. Simpson, S. Mehta, G. Marshall, S.M. Smith, S.R. Zwart, M. Heer, S. Ponomarev, A. Whitmire, J.P. Frippiat, G.L. Douglas, H. Lorenzi, J-I. Buchheim, G. Makedonas, G.S. Ginsburg, C.M. Ott, D.L. Pierson, S.S. Krieger, N. Baecker, C. Sams, Immune System Dysregulation During Spaceflight: Potential Countermeasures for Deep Space Exploration Missions, Frontiers in Immunology, v9 (2018).

[6] N. Yamamoto, K. Otsuka, Y. Kubo, M.i Hayashi, K. Mizuno, H.Ohshima & C. Mukai, Effects of long-term microgravity exposure in space on circadian rhythms of heart rate variability, Chronobiology International , 32:3, (2015) 327-340.

[7] S. Patel, The effects of microgravity and space radiation on cardiovascular health: from low-Earth orbit and beyond. Int. J. Cardiol. Heart Vasc. 2020;30:100595. https://pubmed.ncbi.nlm.nih.gov/32775602/

[8] M. Shelhamer, J. Bloomberg, A. LeBlanc, G.K. Prisk, J. Sibonga, S.M. Smith, S.R. Zwart, P. Norsk, Selected discoveries from human research in space that are relevant to human health on Earth. NPJ Microgravity. 6:5 (2020).

[9] L. Vico, A. Hargens, Skeletal changes during and after spaceflight, Nat Rev Rheumatol 14(4) (2018) 229-245.

[10] A. Niehoff, G.P. Brüggemann, N. Hamann, F. Zaucke, F. Eckstein, W. Bloch, A. Mündermann, S. Koo, J. Mester, A.M. Liphardt, Long-duration space flight and cartilage adaptation: first results on changes in tissue metabolism, Osteoarthritis and Cartilage 24:S (2016) 144-S145.

[11] A. Van Ombergen, S. Jillings, B. Jeurissen, E. Tomilovskaya, R.M. Rühl, A. Rumshiskaya, I. Nosikova, L. Litvinova, J. Annen, E.V. Pechenkova, I.B. Kozlovskaya, S. Sunaert, P.M. Parizel, V. Sinitsyn, S. Laureys, J. Sijbers, P. Zu Eulenburg, F.L. Wuyts, Brain Tissue-Volume Changes in Cosmonauts, New England Journal of Medicine 379(17) (2018) 1678-1680; A. Van Ombergen, S. Jillings, B. Jeurissen, E. Tomilovskaya, A. Rumshiskaya, L. Litvinova, I. Nosikova, E. Pechenkova, I. Rukavishnikov, O. Manko, S. Danylichev, R.M.

Rühl, I.B. Kozlovskaya, S. Sunaert, P.M. Parizel, V. Sinitsyn, S. Laureys, J. Sijbers, P. Zu Eulenburg, F.L. Wuyts, Brain ventricular volume changes induced by long-duration spaceflight, Proceedings of the National Academy of Sciences 116(21) (2019) 10531-10536.

[12] S. Jillings, A. Van Ombergen, E. Tomilovskaya, A. Rumshiskaya, L. Litvinova, I. Nosikova, E. Pechenkova, I. Rukavishnikov, I.B. Kozlovskaya, O. Manko, S. Danilichev, S. Sunaert, P.M. Parizel, V. Sinitsyn, V. Petrovichev, S. Laureys, P. Zu Eulenburg, J. Sijbers, F.L. Wuyts, B. Jeurissen, Macro- and microstructural changes in cosmonauts' brains after long-duration spaceflight, Science Advances, 6(36) (2020)

[13] L. Opsomer, V. Théate, P. Lefèvre, J-L. Thonnard JL, Dexterous Manipulation During Rhythmic Arm Movements in Mars, Moon, and Micro-Gravity. Front. Physiol. 9, (2018) 1–10.

[14] J. Bernard-Espina, D. Dal Canto, M. Beraneck, J. McIntyre, M. Tagliabue, How tilting the head interferes with eye-hand coordination: the role of gravity in visuo-proprioceptive, cross-modal sensory transformations. Front Integr Neurosci 17 (2022).

[15] 14 CFR § 1214.403 - Code of Conduct for the International Space Station Crew. (https://www.law.cornell.edu/cfr/text/14/1214.403)

[16]E.S. Bishop, S. Mostafa, M. Pakvasa, H.H. Luu, M.J. Lee, M.J. Wolf, G.A. Ameer, T.C. He, R.R. Reid, 3-D bioprinting technologies in tissue engineering and regenerative medicine: Current and future trends. Genes Dis. 4(4) (2017) 185-195. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6003668/

[17] A. Elemoso, G. Shalunov, Y.M. Balakhovsky, A.Y. Ostrovskiy, Y.D. Khesuani, 3D Bioprinting: The Roller Coaster Ride to Commercialization. Int J Bioprint. 6(3) (2020) 301.

[18] S. Santoni, S.G. Gugliandolo, M. Sponchioni, M. et al. 3D bioprinting: current status and trends—a guide to the literature and industrial practice. Bio-des. Manuf. 5, 14–42 (2022).

[19] P. Rider, Ž.P. Kačarević, S. Alkildani, S. Retnasingh, M. Barbeck, Mike (2018-10-08). "Bioprinting of tissue engineering scaffolds". Journal of Tissue Engineering, Jan-Dec (2018). https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6176532/

[20]https://bioprinting.ru/press-center/publications/as-a-private-company-develops-breakthrough-technology-print/ accessed 29 December 2022

[21]https://www.nasa.gov/mission_pages/station/research/experiments/explorer/search.html?#q=bioprint&i=&p=&c=&g=&s=&a= accessed 29 December 2022