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Campaign:

NASA Biological and Physical Sciences – High-Quality Cell and Tissue Cultures in Microgravity

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Introduction: Prior spaceflight study results confirm that unique biological phenomena occur in cell and tissue cultures in space. These insights provide an opportunity not only to expand our knowledge of astronaut health and fundamental biology but also to better understand disease biology and create novel products related to disease modeling[1]. While the field of biology in space is still in its infancy, the combination of contemporary and rapidly maturing biotech capabilities on Earth and recent research in space define a priority area for investigation on the International Space Station (ISS) over the next several years. ISS research and demonstration should determine (1) whether scalable, reproducible, iterative, and Good Manufacturing Practice (GMP)-compliant cell and tissue culture can be extended to low Earth orbit (LEO) and lunar environments and (2) how to assess and control the quality of the resulting data and products.

A campaign focused on developing high-quality cell and tissue cultures in microgravity will impact the two-pronged mission of NASA's Division of Biological and Physical Sciences (BPS) to "pioneer scientific discovery in and beyond low Earth orbit to drive advances in science, technology, and space exploration to enhance knowledge, education, innovation, and economic vitality" and to "enable human spaceflight exploration to expand the frontiers of knowledge, capability, and opportunity in space." The campaign will rely heavily on the integration of multidisciplinary expertise. Through this white paper, we outline the rationale for, and current status of, the development of technologies and experiments to validate the production of cellular and multicellular products in LEO and, ultimately, the Moon. We also provide a roadmap for achieving scalable, iterative cell and tissue culture that could be extended to LEO and lunar environments.

Background: The fields of molecular cell biology, tissue engineering, and regenerative medicine have made tremendous strides in the past few decades. These strides are in no small part due to advances in capabilities that allow for the reproducible, iterative, on-demand experimentation needed to validate scientific findings, confirm hypotheses, uncover novel phenomena, and develop commercially viable biological products. Without technologies that allow for these capabilities, advances in scientific understanding as well as regulatory approval would not be possible; instead, we would be reliant on anecdotal information from individual experiments. However, due to the commitment to develop the appropriate tools, we are now at the frontier of seeing FDA approval of cellular products for therapeutic use. For example, the use of CAR-T cells for cancer treatments has been rapidly expanding and is now commercially viable. Additionally, in the last few years, we have seen the onset of clinical trials using cells derived from pluripotent stem cells for the treatment of chronic diseases such as Parkinson's disease[2] and age-related macular degeneration[3].

The intersection of molecular cell biology and spaceflight research (such as the work conducted on the ISS) has also advanced in the past decades, enabling cell culture experiments in the LEO environment to obtain both real-time in-space data as well as data from materials returned to Earth. These capabilities have allowed researchers to ask fundamental questions about how the spaceflight environment affects cellular behavior[4-8]. Additionally, ongoing efforts are aimed at understanding human cellular responses to spaceflight and utilizing the LEO environment for disease modeling (for both the spaceflight-induced effects and terrestrial diseases that spaceflight appears to accelerate) as well as the development of therapeutics and countermeasures[9]. Coupling the data obtained from spaceflight experiments with ground control and simulated spaceflight experiments has led to intriguing observations about the effects of spaceflight on

cellular responses[1,10-14]. However, due to the nature of conducting spaceflight experiments, the results obtained are often the product of a limited sample set and are almost never independently validated in follow-on experiments. These factors limit the impact of the findings and the validation of results, thus restricting potential advancements in the field for both fundamental research as well as the de-risking of exploration goals.

During the last quarter of 2020 and the first quarter of 2021, the Center for the Advancement of Science in Space, Inc. (CASIS), which manages the ISS National Laboratory, and the McGowan Institute for Regenerative Medicine held a Biomanufacturing in Space Symposium. The symposium brought together subject matter experts in stem cell biology, tissue engineering, disease modeling, spaceflight research and development, automation, and the implementation of artificial intelligence (AI) and machine learning (ML). Symposium participants spanned the commercial, academic, and government sectors. Findings that came out of the symposium are discussed in several publications[1,16]. While the focus of the symposium was on the opportunities a LEO-based platform offers for terrestrial commercial impact, many of the findings are of high relevance to NASA BPS and the contents of this campaign white paper. One of the primary conclusions from the symposium was that a significant increase in data generation is needed to draw scientific conclusions and make informed priority decisions[1,16]. This is critical information for the NASA BPS community that is looking to fulfill its mission regarding biological sciences. The campaign outlined in this white paper will close the current gaps by developing technologies, including the application of AI/ML and robotics, aimed at exponentially increasing the cell culture capabilities available in LEO and, eventually, on the lunar surface.

Impact Areas: The following areas of research are just some of the many areas that would be significantly impacted by advances in scalable, reproducible, iterative cell and tissue culture in the LEO and lunar environments. The list is intended to identify areas that align with the NASA BPS mission as well as reach into other government agency priorities and commercial objectives. Note that some of these impact areas and a number of others are presented in greater detail in the perspectives published this year[1,16].

Fundamental Biology and Development. There has been much interest in using microgravity to potentially enhance stem cell properties such as pluripotency and multipotency, proliferation, differentiation, and/or maturation of stem cell derivatives. The ability of microgravity to beneficially alter these stem cell properties is documented in peer-reviewed scientific literature[4-8]. However, a significant and common issue in the stem cell field is variability in stem cell potency and differentiation capacity between cell lines. This often detrimentally influences experimental rigor and reproducibility in academic and clinical applications. Thus, it is critical to identify novel methodologies that will regulate and either maintain or enhance the potency and differentiation capacities of multipotent and pluripotent stem cell lines. These improvements in stem cell properties will impact the biomanufacturing of stem cell-derived products not only from a research and development perspective, where cell expansion is limited on Earth, but also for clinical and therapeutic applications, both terrestrially and in an exploration setting. Similarly, there are tremendous opportunities for understanding the effects of microgravity, and spaceflight in general, on the secretome, which has implications for human health both on Earth and in space exploration[17-18].

Food Production. The large-scale production of food products from cell-based sources has become a significant area of interest within the past decade[19]. Options to create cell-based foods

have emerged due to improvements in the maintenance of primary muscle tissues and adipose tissues from livestock, improvements in meat "analog" production, and the enhancement of differentiation protocols to create food analogues from multipotent and pluripotent stem cells. Food production is also of great interest for exploration missions to the Moon and beyond, as keeping astronauts satiated and both physically and psychologically healthy with nutritious and appetizing foods is critical to mission success. LEO-based production and maintenance of food products will require overcoming multiple logistical hurdles and barriers, such as the requirement of water for food processing, an appropriate means of storing premade meals and de novo LEO meals, and a method for the appropriate disposal and recycling of various food wastes and byproducts. In addition to enabling exploration missions, the technologies needed to maintain and mass-produce food products in LEO could also harbor significant utility for purposes on Earth, such as reduced dependance on natural resources.

Tissue Engineering and Mechanobiology. Engineered tissue constructs are generally fabricated by seeding cells into a biomimetic scaffold and allowing the cells to proliferate, differentiate, and otherwise organize into a 3D structure. However, forcing a tissue to conform to a pre-existing scaffold does not mimic the biological tissue formation enabled by the neutrally buoyant environment of embryogenesis. Alternatively, tissue self-assembly in microgravity allows for complex 3D structures to form spontaneously, eliminating the need for artificial scaffolds and support structures[20-21]. Additionally, LEO provides a unique environment to study the mechanotransduction pathways that mediate responses to changes in gravity, and this is an area of interest currently supported by the U.S. National Science Foundation's use of the ISS[22].

Disease modeling. For a decade, human pluripotent stem cells, especially induced pluripotent stem cells (iSPCs) from individuals whose health records are available, have been proposed as the best solution to accelerating the understanding of human disease and the identification of effective therapies. Animal studies are increasingly being recognized as insufficient for developing safe and effective treatments for human disease. Because of the challenges of culturing iPSCs (which in many ways are unlike any cell type that has been cultured before), progress toward using these cells for disease modeling and therapeutic development has been slow. However, increased experience, along with improvements in reagents and methods, have made it possible to integrate iPSCs into drug development pipelines. Additionally, the effects of spaceflight on model systems provide novel approaches to interrogate accelerated aging and other disease processes that can be leveraged to improve life on Earth. This has been a priority area for the National Institutes of Health in the agency's use of the LEO environment to advance its research goals[9].

Monitoring human health and treating disease in space. Low gravity is known to have effects on multiple organ systems; however, there are significant limitations in what can be measured while astronauts are in space. It will soon be possible to create cell cultures from an astronaut's iPSCs and differentiate them into major cell types, such as hepatocytes, cardiac muscle cells, multiple neuronal cell types, and skeletal muscle cells. Cultures of an astronaut's iPSC-derived organ-specific cell types could accompany an astronaut into space and serve as cultured avatars that can be monitored for changes that may provide early risk predictors that reflect on the health of the astronaut. Additionally, in-space generation of astronaut-derived iPSCs may be used for precision-medicine applications, including selection from and provision of a variety of therapeutic treatments or countermeasures during exploration missions.

Research Questions. In order to develop scalable, reproducible, iterative cell and tissue culture that can be performed in LEO and lunar environments, a number of questions need to be addressed in order to identify the best solutions. These will be developed and informed through campaign semiannual meetings and solicitations. A subset of these questions to be answered includes the following:

- How can cell culture reagents and consumables be effectively stored and controlled for quality? Could an enhanced sterilization and reuse process be implemented for LEO- or lunar-based biomedical research?
- Can reagents (i.e., buffers, media, fixation solutions) and consumables (i.e., culture wells, pipette tips) be manufactured de novo on station from existing supplies?
- How can access to water, specifically sterile water for culture, be maximized? Can media alternatives with more concentrated nutrients be used?
- How can sterile working environments be provided? If pathogenic contamination (e.g., bacterial) is detected in a cellular culture, how can that culture be isolated/terminated effectively and safely to prevent the spread of contamination to other cell cultures? Can special types of pathogen-resistant reagents/media be developed to maintain sterility?
- How can faults/malfunctions in advanced pieces of biomedical research be rapidly, safely, and effectively fixed either automatically or with minimal crew intervention?
- What standards should be adopted for biological selection (i.e., cell source and quality control)? What experiments need to be conducted to validate reproducibility and robustness? Which international standardization bodies should be included?
- What measurements and readouts are needed? How should capabilities be prioritized, and how can maximal flexibility be allowed for?
- How should data be stored and processed for public distribution? Can in-LEO servers and data processing hubs be implemented with AI/ML?
- How will AI/ML tools and robotic automation be implemented to optimize culture and differentiation protocols, enhance experimental reproducibility, enable greater throughput of experimental setups, and minimize crew time?
- What considerations need to be made to utilize next-generation LEO facilities?
- What additional considerations are needed to enable adaptation to lunar-based applications?

Products and Timeline. These research questions and their answers will be addressed through campaign semiannual meetings as well as a series of solicitations. The meetings will be attended by program staff, awardees, and outside subject matter experts. The solicitations will involve awards that are gated. The gated process will allow maximal participation in early rounds and prioritize products and solutions that demonstrate the highest probability of success. The campaign should be structured in a way that provides the potential to combine teams to maximize validated solutions to the following products with tangible outcomes:

Product 1. Iterative Cell Culture: Demonstrate the capability to culture a cellular product (single cell type) three different times (iteratively) without the need to resupply materials. Demonstrate this capability across three different cell types to show robust utility. The capability needs to include inline analysis and sample storage for postflight analysis.

Product 2. Iterative Multi-Cell Culture: Demonstrate the capability to culture a cellular product (consisting of at least three different cell types) three different times (iteratively) without the need to resupply materials. This should include inline analysis and sample storage for postflight analysis.

Product 3. Scalable Multi-Cell Culture: Demonstrate the capability to culture a cellular product (at least three different cell types) three different times in multiple parallel units without the need to resupply materials. For example, running two different units in parallel, with each unit conducting three rounds of cell culture.

Product 4. AI/ML-Enabled Autonomous Cell Culture: Demonstrate the capability to utilize inline AI/ML to autonomously monitor, evaluate, and modify cell culture conditions to achieve an optimal outcome.

The initial solicitation for all of these products will be for ground development of a LEO-viable product. The table notes that for Product 1, 10 awards should be issued for ground development, and it is likely that 8 teams will advance to the next round of solicitations. In this round, the campaign would fund six teams to each begin Product 1 LEO development and Products 2-4 ground development. The year 2027 will include a third of solicitations for Products 2-4 LEO development, with the expectation of awarding two to three teams. It is anticipated that one to two of the teams will complete the LEO-based development. The year 2029 will see the award of one team to begin development of a lunar prototype. The timeline will allow the products to be fully operation in LEO by 2029, permitting extended partnerships between NASA BPS, other government agencies, and commercial partners.

Task	2022	2023	2024	2025	2026	2027	2028	2029	2030	2031	2032
Meeting	2	2	2	2	2	2	2	2	2	2	2
Product 1		10(8)			6(2-3)			1			
Product 2				6(2-3)		2-3(1-2)					
Product 3				6(2-3)		2-3(1-2)					
Product 4				6(2-3)		2-3(1-2)					

Table 1. Timeline for campaign. Color key: Green = meeting; Blue = solicitation for ground development; Orange = solicitation for LEO development; Salmon = solicitation for lunar prototype; # outside () = number of awards; # inside () = anticipated number to complete phase

Conclusion: It is important to note that many of these products have been developed for terrestrial applications and are continually being optimized. Thus, the knowledge base is available, but the challenge will be to implement the products in the LEO environment and beyond. We believe that wherever possible, terrestrial products and standards should be implemented to maximize translatability. Finally, we are confident that technologies developed through this campaign will reciprocally have a significant impact on terrestrial technology development in areas such as automation, miniaturization, AI, robotics, and waste reduction.

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