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# International Space Omics Processing Standards

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**ABSTRACT:** In order to get ready for Mars, space organisations have announced plans for human expeditions to the Moon. Radiation, microgravity, and solitude are among the stressors that the space environment provides. For crewed space exploration to be successful and safe, it is essential to comprehend how these elements affect biology. Developing defences, modifying plants and bacteria for food supplies and bioregenerative life support, and reducing pathogen infection are all necessary. Space omics research is being done by scientists all over the world on model organisms and, more lately, on people. It will take improved standardisation for these priceless datasets to be optimally mined for scientific findings that can be put into practise. Researcher created ISSOP (International Standards for Space Omics Processing), an international partnership of scientists, to solve this deficiency by enhancing global standards among space biologists. Here, we describe our consortium and discuss the spaceflight omics-related issues we've faced in the past.

**KEYWORDS:** Neuro-Ophthalmic disorders, Long Term space Travel, Space Omics, Vestibular Control, ISS

## I. INTRODUCTION

In order to get ready for the first crewed flights to Mars, space organisations have announced plans to return people to the Moon. This marks the beginning of a new era for deep space travel for humanity. Some of the known stresses on people in the space environment include radiation, microgravity, changing atmospheric gas composition, isolation, and dietary changes; these variables are anticipated to worsen with mission duration and distance outside of low Earth orbit. Negative impacts on human health during spaceflight include immune system suppression, skeletal muscle atrophy, cardiovascular deconditioning, vestibular control, bone demineralization, neuro- ophthalmic disorders, and immune system suppression. 9 To provide the safeguards required for safe and successful crewed space flights, it is imperative to better understand how spaceflight elements affect human health. Furthermore, essential components of the infrastructure for space exploration, such as food and medical supplies, are insufficient for lengthy trips. 10 The National Aeronautics and Space Administration (NASA) Twins Study provided additional evidence of the necessity for thorough, consensus-based methods to investigate the long-term impacts of human spaceflight. 11 A multi-omics synthesis was carried out by a tenth research group in order to provide a systematic whole-body layout of the modifications, whereas nine research groups carefully examined one data type in this case. Telomere length, gene regulation, gut microbiome composition, body weight, carotid artery diameters, and serum metabolite profiles were among the many data types the study discovered to have changed. Some of these alterations continued for more than six months after returning to Earth, albeit many of them were just temporary. 11 The NASA Twins Study is a significant advancement in space biology research, but it is also unusual. Model organisms are used to create the vast majority of space biology experiments and databases (Figure 1). Microbes are studied to understand how space affects human microbiomes, plant-microbe interactions, and environmental cleanliness, while also advancing the fields of space biotechnology, planetary protection, and astrobiology. Animal models are used to infer how spaceflight affects humans. Plant models are used to elicit how crops can be grown in space for food and renewed oxygen sources. 12,13 Due to its capacity to optimise the knowledge obtained from unique spaceflight studies, omics techniques are becoming more and more important to space biologists worldwide (Figure S1). This encompasses metabolomics, metagenomics, transcriptomics, proteomics, and epigenomics. 11 While omics can provide enormous amounts of data that may pave



the path for successful space missions, the best extraction of useful scientific insights from these complicated data will only happen with increased international standardisation and communication. In recent years, a number of consortiums have been established to address the biological data's rising cost, size, and complexity. 35–41 These committees put policies into place that markedly hastened the advancement of science in their respective fields. The space omics community can borrow successful frameworks from these role models as it is still a young field. However, the principles established by these groups cannot be directly transferred to the field of space omics. To ensure the success of biological research conducted in spaceflight, the international space biology community will need to particularly address the special technical and biological hurdles that must be overcome. In response, we established the International Standards for Space Omics Processing collaboration (ISSOP). Our members are researchers who work on space omics projects supported by numerous space agencies in the US, Europe, Japan (JAXA), and Europe (including representatives from the European Space Agency [ESA] Space Omics Topical Team<sup>42</sup>) (NASA). We contribute expertise in space biology's use of multi-omics and systems biology techniques, the normalisation of spaceflight metadata, and the processing of space omics samples from humans, vertebrate and invertebrate model animals, plants, and microbes. We are also kept up to date on the most recent developments in politics, business, and academics. Our goal is to create, promote, and share sample-processing standardisation and metadata normalisation of spaceflight omics investigations in order to improve data harmonisation and knowledge acquisition. In the first section of this study, we provide instances of previous lessons discovered through omics research on model organisms in space. These instances highlight the distinct technological and biological difficulties that come with carrying out spaceflight omics and highlight the need for further standardisation in the field. We then declare that ISSOP is now being formed to fulfil these demands on a global scale. We conclude with a brief section on potential future directions for ISSOP to advance the field of space omics through the application of standardised and systematic science.

## II. SPACE OMICS WITH MODEL ORGANISMS

Each stage of a space omics experiment has its own special difficulties. Here, we list those issues and any solutions that have come forth as a result of model organism research in recent years. In roughly the same order of steps as space omics research is conducted, we proceed through this part. Planning spaceflight experiments presents new technical challenges to the space omics community. Logistical constraints in terms of time, money, and space are among the most basic difficulties. First, the number of experimental repetitions and variables are constrained by the capacity of orbiting platforms, particularly for rodent and plant investigations. Small replicate numbers limit strain diversity and statistical power. Long-term space missions will require genetically diversified crops to support robust bioregenerative life support systems; yet, most plant species investigated in space have been restricted to low biomass species due to volume restrictions. 43 Secondly, crew time is extremely constrained for experimental spaceflight techniques. The cost of an astronaut's time in 2019 was \$17,500,44 whereas the mean hourly income for biochemists and biophysicists in the United States was \$52.01.45 These figures generally indicate that conducting research in space can cost more than 300 times as much as doing it on Earth. On the ISS, some procedures are challenging because of the limited crew size, lack of laboratory expertise, and lack of equipment compared to what is typical in terrestrial laboratories. Third, because of logistical and financial limitations, repeating unsuccessful tests and following up successful studies are both challenging. In addition, waiting periods are often substantially longer compared to experiments conducted on the ground.43

## III. HOUSING AND HARDWARE

Rarely are biological investigations carried out in space using conventional ground technology. It is a continuous struggle to create specialised hardware and housing technology that can function in spaceflight conditions. Several systems for studying animal and plant physiology in space have been developed over the last few decades. 46–49 With these technological developments, it has become obvious that the hardware itself and the way it is used in experimental design need to be meticulously standardised and iteratively improved in order to eliminate unintentional confounding variables as they are better understood. The typical mouse vivarium cages employed in ground research, for instance, are inappropriate in microgravity. The NASA Animal Enclosure Model is one piece of hardware that has shown to be a successful platform for rodent investigations while in space (AEM). 49 In a recent meta-study, all datasets in the NASA GeneLab database that contained samples for both conditions were compared, allowing for a comparison of AEM ground controls and vivarium ground controls. 50 When only the habitat was altered, the authors' unbiased systems biology method found significant transcriptional differences in ground control rodents. 50 Particularly, a moderate hypoxic phenotype was seen in the AEM condition, which may have been caused by the device's deliberate design to passively absorb increased CO<sub>2</sub> concentrations added to replicate the atmosphere of spaceflight. 50 Importantly,





elevated CO<sub>2</sub> levels may make people more prone to headaches and lower their cognitive scores. 51,52 Overall, this work emphasised the crucial necessity for carefully planned ground control trials to address confounders that could otherwise result in inaccurate results about the omics impacts of spaceflight, something that has also been shown in flies cultured in space. Additionally, 25 Plants need specialised hardware designs for spaceflight, some of which have been used frequently enough for experts to recognise that the hardware itself introduces unneeded variables. For instance, astrobotany tests using the Biological Research in Canisters (BRIC) technology, which needed no power and only a little amount of crew time, revealed a number of shortcomings. Due in part to an etiolated reaction to its dark environment, the hardware itself caused a reduction in the size of plant endodermal cells. 53 The BRIC Petri Dish Fixation Unit (BRIC-PDFU) hardware similarly induces stress-related alterations in the transcriptome and proteome of Arabidopsis seedlings, emphasising the ongoing need for iterative hardware updates going forward. 54 The spaceflight industry updates gear not only to enhance design but also to incorporate fresh features that save crew members' time and effort. Real-time imaging, ground commanding, and automated software are some of these features. To more clearly distinguish between the accumulative impacts of living in space, new characteristics have also been included. For instance, the European KUBIK incubator and the JAXA Multiple Artificial-Gravity Research System (MARS) platforms both offer 1g in-flight controls, unlike the NASA BRIC and BRIC-PDFU platforms. 15 The risk of misidentifying omics results as responsive to microgravity exposure when they are actually relevant to other spaceflight variables may be reduced by these controls. However, we observe that these platforms inherently present their own perplexing influences, as is the case with the majority of cutting-edge spacecraft dwelling units. Particularly, the rotor system has gravity gradients, and sample sites do not experience the same gravity force. It is crucial for plant biologists who utilise these platforms to provide metadata that includes both nominal partial g and real partial g for each sample site since tiny variations in partial gravity exposure result in significant changes in transcriptional patterns in plants<sup>55,56</sup>. It is well known that both on Earth and in orbit, dependable 1g controls are used. 24,57,58 It is possible to analyse the distinctive contributions of each confounding element generated by spaceflight or hardware requirements using a wide range of ground-based simulation systems<sup>55</sup>. The rotating wall vessels (RWVs), 2D clinostats, random positioning machines (RPMs), and diamagnetic levitation are examples of microgravity simulators. 59 Each of these simulators introduces unique artefacts. Clinostats, for example, cause centrifugal accelerations and vibrations, while diamagnetic levitation alters the behaviour of cell components depending on magnetic fields. 59 For these reasons, uniform terminology must be employed and standards must be put out for various simulators and operational modes. 59 According to scientists, commercial systems like Tan-goLabs (Space Tango, Lexington, KY), NanoLabs (NanoRacks, Houston, TX), and ICE Cubes Facilities are increasingly being used for biological investigations in space (Space Application Services, Sint-Stevens-Woluwe, Belgium). Communication will become more and more important between the academic, governmental, and industry sectors researching and refining hardware designs in order to increase standardisation and exchange lessons gained. For accurate interpretation of space omics data, it will also be essential to collect metadata consistently about the gear being used.

#### IV. COLLECTION AND STORAGE OF SAMPLES

Since even small fluctuations in partial gravity exposure result in large changes in transcriptional patterns in plants<sup>55,56</sup>, it is essential for plant scientists using these platforms to supply information that includes both nominal partial g and real partial g for each sample site. It is commonly known that reliable 1g controllers are utilised on Earth and in orbit. 24,57,58 A variety of ground-based simulation systems<sup>55</sup> can be used to analyse the unique contributions of each confounding factor caused by hardware requirements or spaceflight. Examples of microgravity simulators include rotating wall vessels (RWVs), 2D clinostats, random positioning machines (RPMs), and diamagnetic levitation. 59 These simulators all present different artefacts. For instance, clinostats create centrifugal accelerations and vibrations, while diamagnetic levitation modifies how magnetic fields affect the behaviour of cell components. Critical metadata is linked to each dataset via GeneLab. Biology factors (such as age, gender, strain, and ecotype), lifestyle factors (such as diet, exercise, and light cycle), experimental design factors (such as hardware and pre- and post-flight exposure to stressors), sample-processing factors (such as preservation methods and library preparation methods), and spaceflight factors are just a few of the many confounding variables that may be present during space omics experiments (such as gravity, atmospheric pressure, temperature, and ionising radiation). In general, information can be methodically investigated to build strong networks that anticipate confounding variables and ultimately identify new experimental and engineering improvement areas for spaceflight omics studies. 67 The field of space biology is always improving its metadata procedures. Space omics data, for instance, now includes ISS environmental metadata (such CO<sub>2</sub>, temperature, and radiation levels). 68 Space omics investigations sometimes do not have dosimeters in their housing units, therefore dose exposure for study samples must be inferred from surrounding dosimeters. 68 Careful metadata standardisation efforts will advance and address these problems. Additionally, external tools are being created



to improve metadata discoverability and reproducibility. A cross-species transcriptional viewer (NASA GeneLab Cross Kingdom Database) and a metadata visualisation API for the GeneLab platform called TOAST (Test of Arabidopsis Space Transcriptome) were created by the Gilroy Astrobiology Team at the University of Wisconsin. These tools use iterative methods to help users identify shared gene clusters among space omics datasets. 68 Space biologists use established ontological vocabulary that are recognised by the greater scientific community as part of the Ontology for Biomedical Investigations as much as possible (OBI). However, nomenclature must occasionally be expanded from the OBI due to the novel nature of space biology. This has been the case, particularly for topics related to radiobiology and space radiation. In order to provide regulated integration across datasets and metadata sources, new ontology concepts must be added with caution. 69 Another laborious manual task is normalising metadata, which occasionally necessitates speaking with principle investigators and reading books to gather necessary data. This ambitious attempt cannot be scaled out to handle the increasing amounts of incoming space omics datasets. 69 In the future, submission portals can be developed to boost automatic curation, which has already shown to be largely successful in applications outside of spaceflight. 69 Algorithms can direct data submitters to include important information and even give justifications for why specific meta-data is necessary. Researchers' adherence to metadata submission requirements will increase if the significance of space omics confounders is well communicated to them. This will increase the automation of metadata curation and the validity of cross-data studies. Recent studies have shown the effectiveness of combining various datasets from the GeneLab database to trigger systemic, global responses to the space environment. 50 Future research can use the database and its comprehensive metadata in a similar way to achieve the bigger sample numbers and more powerful statistical capabilities required to further uncover important elements affecting organisms which flown into space.

## V. SAMPLE TRANSFER

It's unlikely that a single study team will be able to understand basic molecular reactions to space. To promote discoverability and reproducibility among researchers in the field of space omics, sample-sharing protocols must be improved. Sharing a single biobank and sample-processing facility is excellent for this purpose. Researchers may avoid conducting repeated, resource-intensive experiments in space by checking to see if tissues of interest are already available from earlier studies thanks to a structured, user-friendly biobank. Batch effects that might normally be introduced in a multiple-facility configuration can be avoided with a central sample-processing facility. Using standard operating procedures (SOPs) carried out by professionally trained laboratory operators and robotic workstations, the shared facility can provide high-quality data. This architecture would, in general, be consistent with successful multi-omics initiatives like the TCGA project, where each type of omics was controlled by a single centre. 36 Thankfully, Japan and the US have already implemented space economy-sharing programmes. A typical JAXA mouse live animal return study uses 12 mice, which produce more than 30 different tissue types using a variety of omics assays. More than 10 primary scientists then exchange their findings. A common lab at the University of Tsukuba uses LabDroids to automate sample processing as it processes genomic data from spaceflight mice. 70 The NASA Biospecimen Sharing Program of the Life Sciences Data Archive frequently houses unused frozen spaceflight samples from earlier experiments. These samples are processed by GeneLab scientists at the sample-processing lab using standardised procedures to ensure data reproducibility. ESA does not have its own sample-sharing programmes, but it does support international spaceflight experiments involving sample sharing among European academics and it engages in bilateral cooperation with JAXA and NASA programmes. Valuable sharing arrangements for these uncommon and expensive biological samples sent from space should keep getting better as the discipline develops.

## VI. PRESENT NEED FOR A GLOBAL CONSORTIUM

We have organised to develop guidelines for space omics data with participation from scientists globally due to the growing reliance on and promise of omics technologies when properly standardised and the provision of unique expertise by various governments. As the field of human space omics develops, we hope that our principles will be easily applied to people from animal models, specifically allowing for comparable inference and comparison across data from human and animal models. As they are created and regularly updated, our most recent protocols will be accessible on the websites of our consortium (<https://issop.space>) and ISSOP (<https://github.com/ISSOP>).

## VII. FUTURE ROUTES

In this study, we examined the difficulties of doing omics research on model organisms in space. The field can be advanced most effectively by an international group of scientists with experience in space omics investigations across a



variety of assay types and model organisms. ISSOP can create suggestions for space omics across many assays, such as proteomics, metabolomics, metagenomics, transcriptomics, and epigenomics, in future studies. For less well-known yet potential molecular biology laboratory procedures, guidelines can also be produced. For instance, laser microdissection (LMD) and spatial transcriptomics are currently being used in NASA and JAXA projects to collect data at the tissue-part level as opposed to only the tissue level. Participants in these studies from ISSOP can create standardisation guidelines for space omics. For different creatures, best practises can also be suggested. For instance, as was already indicated, physical limitations on orbit limit the number of samples that may be taken from some organisms, including plants. Astrobotany-trained ISSOP members can advise on standards to extract the most data possible from sparse samples while in orbit. One of the key elements for future remote experiments and project sharing will be the digitization of sample handling with cutting-edge robotics. Overall, ISSOP can offer varied and well-balanced recommendations for carrying out omics experiments in space using a variety of assay types and model organisms; these recommendations can include quantitative and qualitative details about data gathering, data extraction, library preparation, quality control, sample preservation, and sequencing parameters. This data may one day be combined into a proto-col decision tree algorithm that may offer principal investigators uniform recommendations depending on their target species and assays. As we enter the era of human space omics, the problems outlined in this paper will become even more acute. Commercial spaceflight will cause a greater spectrum of health conditions in humans to enter space, and long-duration deep space missions in the future will expose people to more acute environmental stresses for longer periods of time than before. For these ambitious frontiers, the space telemedicine sector will need to be fine-tuned, and omics will work best when added as a regular measurements programme. Due to the complexity of the technology and the cultural ethics of working with human subjects, first crewed missions to Mars will probably involve international input. For an impending era of human space omics, ISSOP may be well positioned to take advantage of the knowledge gained thus far from model organisms and create an informed framework early on that can optimise scientific discovery and reduce ethical issues. It is compelling to believe that careful standardisation of space omics data through IS- SOP may open the door to cell space atlases<sup>72,73</sup> and precision spaceflight medicine<sup>74–78</sup>, which will significantly increase the safety of astronauts. Here, we've introduced ISSOP as a global organisation that can help researchers gain the most useful information from space omics data through increased standardisation, all while assisting prospective ground-breaking space missions at this crucial time. The goal of this study is to educate scientists and data scientists from a wide range of disciplines about the difficulties and potential future developments in the fascinating topic of space omics. This article can also be used as an introduction resource for newcomers to the field of space omics and wider space biology. We encourage curious readers to visit our website to find out more information about ISSOP. Following the satellite ISSOP publications will be additional in-depth analyses of particular areas of conventional space omics processing, all with the goal of advancing our knowledge of the omics consequences of spaceflight so that mankind can safely explore new planets.

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