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Global Space Omics Processing Standards

Dr Debopriya Ghosh[1], Dr Stephen Gershman, Dr Timothy Anderson, Mr. Peter,

Department of Physiology, University College of Medical Sciences. Delhi, India.

Department of Neuroscience, University of Alberta, Canada.

Department of Robotics, Purdue University, USA.

International Space University, France

ABSTRACT: In order to get ready for Mars, space organisations have revealed plans for human expeditions to the Moon. Radiation, microgravity, and solitude are among the stresses that the space environment provides. For crewed space travel to be successful and safe, it is essential to comprehend how these elements impact 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 around the world on model organisms and, more lately, on people. It will need increased standards for these priceless datasets to be optimally mined for scientific findings that can be put into practise. Here, we describe the global collaboration and discuss the spaceflight omics-related issues we've studied in the past.

KEYWORDS: Space Omics, ISS, Long Term Space Travel, Bioregenarative life Support.

I. INTRODUCTION

The announcement by space agencies to return people to the Moon in advance of the first crewed flights to Mars heralds the beginning of a new era in human deep space exploration. Some of the recognised 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 influence 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 more 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. Microbes are studied to comprehend 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. 12,13The zebrafish, medaka fish, fruit fly, and worm have all been useful models for studying the effects of micro- gravity (mg), hypergravity, and space stressors using much larger sample size17–24 and proper 1g controls in space via centrifuges and on the ground via microgravity simulator. More specifically, the NASA Rodent Research (RR)14 and Japan Aerospace Exploration Agency (JAXA) Mouse Habitat Unit (MHU)15,16 series are part of 34 Due to its capacity to optimise the knowledge obtained from rare spaceflight studies, omics techniques are becoming more and more important to space biologists worldwide. This encompasses metabolomics, metagenomics, transcriptomics, proteomics,

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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 standards and communication. In recent years, a number of consortiums have been established to handle 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 organisations cannot be directly transferred to the field of space omics. To ensure the success of biological research conducted in spaceflight, the worldwide space biology community will need to particularly address the special technological and biological hurdles that must be overcome.In response, we established the International Standards for Space Omics Processing collaboration (ISSOP). Our members include researchers who work on space omics projects supported by many space agencies in the US, Europe, Japan (JAXA), and Europe (including representatives from the European Space Agency [ESA] Space Omics Topical Team42) (NASA). We contribute expertise in space biology's use of multi-omics and systems biology techniques, the standardisation of spaceflight information, and the processing of space omics samples from humans, vertebrate and invertebrate model animals, plants, and microorganisms. 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 standards 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 area of space omics through the use of standardised and systematic research.

II. SPACE OMICS

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. We go through this part in nearly the same sequence as space omics research projects are carried out by researchers. Planning spaceflight experiments presents new technological 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 duplicate counts reduce strain diversity and statistical power. Long-term space missions will require genetically diversified crops to sustain 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 suggest that conducting research in space can cost more than 300 times as much as doing it on Earth. On the ISS, several operations are challenging because of the limited crew number, lack of laboratory expertise, and lack of equipment compared to what is typical in terrestrial laboratories. Third, because to logistical and budgetary limitations, repeating failing experiments and following up successful studies are both challenging. Additionally, waiting periods are often considerably longer than they are for tests that are conducted on the ground. 43 Rarely are biological investigations carried out in space using conventional ground technology. It is a continuous struggle to create specialised hardware and housing technologies that can function under spaceflight conditions. Several systems for studying animal and plant physiology in space have been created during 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 inadvertent confounding variables as they are better understood. The typical mouse vivarium cages employed in terrestrial research, for instance, are inappropriate in microgravity. The NASA Animal Enclosure Model is one piece of gear that has shown to be a successful platform for rodent investigations while in orbit (AEM). 49 In a recent meta-study, all records 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 just the environment was changed, the scientists' unbiased systems biology method found significant transcriptional variations in ground control rats. 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 CO2 concentrations added to

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replicate the atmosphere of spaceflight. 50 Importantly, elevated CO2 levels may make people more prone to headaches and lower their cognitive scores. 51,52 Overall, this work emphasised the crucial necessity for well planned ground control trials to address confounders that may otherwise result in inaccurate results regarding the omics impacts of spaceflight, something that has also been shown in flies cultured in space. 25 Additionally, plants need specialised hardware designs for spaceflight, some of which have been utilised to the point where it is clear that the gear itself introduces additional 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 surroundings, 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 just to enhance design but also to incorporate fresh features that save crew members' time and effort. Real-time imagery, ground controlling, and automated software are some of these characteristics. 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 These safeguards may lessen the chance of mistakingly attributing omics findings to microgravity exposure when they are actually related to other spaceflight factors. However, we see that these platforms inherently present their own perplexing influences, as is the case with the majority of cutting-edge spaceship dwelling units. Particularly, the rotor system has gravity gradients, and sample sites do not receive the same gravity force. It is crucial for plant biologists who utilise these platforms to provide information that includes both nominal partial g and real partial g for each sample site since modest variations in partial gravity exposure produce significant changes in transcriptional patterns in plants55,56. It is well known that both on Earth and in space, 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 systems55. 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. It is crucial for plant biologists who utilise these platforms to provide information that includes both nominal partial g and real partial g for each sample site since modest variations in partial gravity exposure produce significant changes in transcriptional patterns in plants55,56. It is well known that both on Earth and in space, 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 systems55. The rotating wall vessels (RWVs), 2D clinostats, random positioning machines (RPMs), and diamagnetic levitation are examples of microgravity simulators. 59 Every one of these simulators introduces distinctive artefacts; for example, clinostats provide centrifugal accelerations and vibrations, and diamagnetic levitation has an impact on cell components that varies depending on the kind of cell. Inconsistencies have developed in the methods used to collect samples for analysis, partially as a result of crew time and financial constraints. For instance, in certain rat experiments, mice are euthanized in orbit (referred to as the "ISS terminal") and then either stored as entire frozen carcasses for later dissection on Earth or dissected right away by astronauts (referred to as the "ISS terminal dissected return"). Animals may also be sent back to Earth alive for euthanasia and dissection (known as a "live animal return"). Each approach has advantages and disadvantages: Live animal return avoids the time and specialised training astronauts would need to do delicate anatomical dissection on the ISS and ensures that these treatments are instead carried out by qualified personnel on Earth. ISS-terminal techniques directly address spaceflight reactions. Scientists may investigate rehabilitation to Earth circumstances and the progeny of returned space-flight mice by returning live animals. On the negative side, pressures applied during reentry, reacclimatization to Earth's circumstances after splashdown and before dissection, and variations in circadian rhythms complicate live anatomical return. Capturing unaltered biological responses to the orbital environment is hampered by the ongoing difficulty of sample preservation aboard the ISS. The current tissue freezing norm on the ISS is —80°C slow freezing due to a lack of access to liquid nitrogen. Unfortunately, NASA Rodent Research-1 (RR-1) flights found that gradual freezing might compromise the accuracy of space mouse gene expression studies. 14 In fact, as compared to mice dissected by astronauts in space, substantial gene expression changes were seen in mouse corpses that were slowly frozen in orbit for later dissection on Earth (ISS terminal frozen return samples) (ISS terminal dissected return samples). This looked to be made worse by

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the RNA sequencing (RNA-seq) methodology based on poly(A) enrichment, but it may be improved by using a ribodepletion-based strategy and snap-freezing car-casses in liquid nitrogen. 60 The Rapid Freeze gear was consequently created lately for usage on the ISS. At speeds comparable to those achieved with liquid nitrogen immersion, the device can freeze mouse tissues (Glovebox freezer) and whole carcasses (Cryochil- ler). Studies are still being conducted to see how this new gear stacks up against the accepted ISS practises. To prevent sample deterioration, RNAlater contains quaternary ammonium sulphates and cesium sulphates, which denature and inactivate ribonucleases. As a fixative that effectively maintains nucleic acids and is regarded as safe in the orbital environment, it has been utilised extensively in space omics. However, a secondary control research discovered that RNAlater exhibits more dramatic differential expression than microgravity does for several genes discovered in spaceflight investigations. 61 The fixation process does not occur quickly enough to stop plants or invertebrates from reacting to the preservative. Under normal circumstances, the preservation effects would be explained by concurrent fixation of the treatment and control samples. The fixation process is expected to be significantly affected in microgravity, which results in sweeping adjustments to structural components of plants and invertebrates as well as variations in fluid dynamics. However, spaceflight is by no means a normal situation. Ultimately, snap-freezing preservation should be used in preference for transcriptome investigations carried out aboard the ISS. To rule out putative fixative-induced transcriptome events in the absence of snap-freezing capabilities, experimenters should compare the overlap in response to RNAlater and their experimental treatments. 61,62 Our comprehension of complicated biology has been greatly improved by the Cancer Genome Atlas (TCGA) project's thoroughly maintained and freely accessible multiomics database. 36 The space omics community must embody this ethos and build a comparable database customised to the particular properties of space omics data in order to understand how biology reacts to space variables. The goal of NASA GeneLab, the first in-depth space omics database, is to maximise the scientific value of spaceflight and ground simulation research supported by several international space organisations. 63 More than 300 transcriptomic, epigenomic, proteomic, metabolomic, and metagenomic datasets from plant, animal, and microbial space investigations are now kept in the archive. Users have unrestricted access to omics data that is pertinent to spaceflight and can upload, download, store, and study it. GeneLab stores raw, intermediate, and completely processed data files and adheres with the FAIR (findability, accessibility, interoperability, and reusability) principles 64, 65. As a result, scientists at all levels and citizen scientists may now access the data. Users can start at any point in the pipeline and thoroughly replicate each stage of the analytic workflow before reanalyzing the data using their choice bioinformatics tools. Processed data files include user-friendly menus that enable users to quickly investigate statistical comparisons and data visualisations in order to produce new space biology theories at high and connected levels, whereas raw and intermediate files lack interpretable biological meaning. 66 A database's power is larger than the sum of its constituent datasets, but only if those datasets can be intelligently cross-examined to help in pattern identification. Datasets called metadata are those that include information about other datasets and serve as the foundation for intelligently linking datasets. Implementing best practises for metadata is therefore just as crucial as it is for the datasets themselves. 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 may be methodically investigated to build strong networks that anticipate confounding variables and ultimately identify new experimental and engineering improvement areas for spaceflight omics investigations. 67 The field of space biology is always improving its metadata procedures. Space omics data, for instance, now includes ISS environmental metadata (such CO2, temperature, and radiation levels). The dose exposure for research samples must thus be inferred from surrounding dosimeters as dosimeters are not normally included in the housing units of space omics investigations. 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 feasible (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

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radiation. In order to provide regulated integration between datasets and metadata sources, new ontology words must be carefully added. 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 information. 69 In the future, submission portals can be developed to boost automatic curation, which has already shown to be mostly effective 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 spatial 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 may make use of the database and its comprehensive metadata in a similar way to get the bigger sample sizes and more powerful statistical analyses required to further find important characteristics impacting space-flying species. It's unlikely that a single study team will be able to understand basic chemical 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 doing repeated, resource-intensive experiments in space by checking to see whether tissues of interest are already accessible 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 research uses 12 mice, which produce more than 30 distinct tissue types using a variety of omics tests. More than 10 main 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 in the sample-processing lab, who produce omics data using established procedures to ensure data reproducibility. ESA does not have its own sample-sharing programmes, but it does support international space investigations including sample exchanges amongst researchers in Europe 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.

III. FUTURE ROUTES

In this study, we reviewed the difficulties of doing omics research on model organisms in space. The field may be advanced most effectively by an international group of scientists with experience in space omics investigations across a variety of assay types and model species. 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 now 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 research can create standardised 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 species, 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 using cutting-edge robots. 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 tests.As we enter the era of human space omics, the problems outlined in this study will become much more acute. Commercial spaceflight will cause a greater spectrum of health conditions in humans to reach 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.

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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 trips to Mars will probably involve international input. For an impending era of human space omics, ISSOP may be well positioned to take use of the knowledge gained thus far from model organisms and create an educated framework early on that can optimise scientific discovery and reduce ethical issues. It is compelling to speculate that rigorous standardisation of space omics data through IS-SOP may open the door to the development of cell space atlases and precision space medicine, both of which will significantly increase the safety of astronauts. 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 may also be used as an introduction resource for newcomers and students to the fields of space omics and wider space biology.

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