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Research Campaign

Title: "Omics" technologies and end-to-end workflows for space-based platforms

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Abstract:
In-space multi-omics technologies and end-to-end workflows on par with those available on Earth are essential to effectively interrogate the etiological effects of microgravity and the space environment on biological systems across the taxonomic spectrum of life forms. We propose a research campaign to achieve these goals in partnership with public and private entities as we work towards creating a space-based economy in the "New Space" age. Building a foundation of core omics technologies for in-space use is a first step towards leveraging the space environment for more advanced applications.

Topics addressed:
Multi-omics technology and workflow development for space.

Introduction:

The harsh space environment results in numerous hazards to human health [1]. Conversely, the space environment is proving to be a tool for discovery research and manufacturing, especially in regenerative medicine [2]. It is important to understand the impact of microgravity and the space environment on living systems for the purposes of developing countermeasures for future deep space missions, as well as to leverage space as a research and manufacturing tool to benefit humanity back on Earth. For this, a fundamental understanding of molecular mechanisms at the genetic level must be acquired while minimizing confounding variables. To achieve these goals, an important first step involves identifying and developing capabilities for use in-space with applications that enable deep insights into the genome and its downstream products, RNA and proteins. Alternatively, existing terrestrial state-of-the-art technologies can be adapted for off-Earth space platforms, such as commercial space stations, which would serve to: (a) achieve NASA's Biological and Physical Sciences objectives more rapidly and with greater precision, (b) attract private sector companies that are leading innovative product development to develop these capabilities for orbital platforms, and (c) create a thriving economy off the planet in LEO and beyond.

The space ecosystem has evolved considerably since the writing of the last decadal survey whitepapers in 2011 [3]. Yet, NASA remains steadfast in its commitment to advancing the nation's science, working towards breakthroughs and discoveries which inform our understanding of the short- and long-term effects of the space environment on living organisms. NASA is leading the innovative and sustainable program of space exploration jointly with commercial and international partners and with the collective goal of enabling human expansion across the solar system [4]. Objectives of the Space Biology Program towards achieving this vision and mission include: (a) discovering how biological systems respond to the space environment, (b) identifying the underlying mechanisms for these responses, (c) understanding and countering these biological mechanisms to support human health in space [5].

Given that DNA is the primary unit of heredity in all living organisms (from microbes to fungi and plants to invertebrates and vertebrates) and codes for the genetic blueprint of life, and that:

(a) environmental factors affect gene expression in biological systems;
(b) microgravity and other space environment factors have demonstrated to affect biological systems;

taking a multi-omics approach to probe the central dogma of molecular biology (genome to transcriptome to proteome) towards the goal of illuminating the etiology of these responses to the space and microgravity environment is an important undertaking to successfully achieve the aforementioned Space Biology Program objectives [6].

Furthermore, considering the rapidly evolving technological landscape in the "omics" arena together with the New Space [7] ecosystem, how can NASA align its objectives with players from both the private and public sectors? For example:

- How can NASA leverage the private sector to develop state-of-the-art biotechnologies, reagents, consumables, tools, diagnostics, and devices for *in-space* applications while also aligning with the private sector objectives to further NASA's vision and mission stated above?

- Conversely, how can NASA's vision and mission further the goals of commercial New Space with respect to new market development and creation of a thriving economy in Low Earth Orbit, the Moon, and beyond?

A coordinated research campaign focused on developing end-to-end multi-omics processing capabilities in space will address both government (NASA) and commercial sector objectives (e.g. expanded market opportunities, new lines of revenue) while also contributing to the development of ground to space value chains of a future space ecosystem and economy. Here, we provide a brief background on the importance of a multi-omics approach, the current omics trends on Earth, the "state-of-the-art" in space, key omics gaps in the space ecosystem, and a road map to filling those gaps.

Key trends in omics on Earth. 1990 marked the beginning of the $3B Human Genome Project as well as the launch of the "omics revolution". Now, 20 years after the completion of the first human reference genome sequence in 2003, whole genome sequencing costs have reduced to less than $1000 per genome and Human Genome Project continues to exert direct and indirect multi-dimensional impacts on biomedical research, human health, technology innovation, and the global economy [8]–[12]. For example, sequencing of the human genome has resulted in the ability to diagnose diseases and disorders, genetic screenings to identify predisposition to diseases, rational drug development, in-silico drug design, gene editing and therapy, human-microbe interaction, personalized medicine, and environmental genomics to name a few [11]. Separately omics has launched new markets such as consumer genomics, and new technologies such as next-gen sequencing, single-cell sequencing, spatial transcriptomics, an entire field of microbiome research, as well as new pathways to studying disease via "multi-omics". Multi-omics, simply defined as the combination of two or more "omics" data sets, enables a more granular probe of the central dogma of molecular biology (i.e., genomics, transcriptomics, and proteomics) to elucidate fundamental disease mechanisms and ultimately develop targeted, effective therapeutics. For example, the advancement in multi-omics technologies has played an instrumental role in the rapid development of COVID-19 therapeutics from the bench to the bedside [13].

Not only is the multi-dimensional approach of multi-omics important for successful translational research, but also for a contextual understanding of cellular processes and signaling pathways at a higher resolution and granular level for *precision* medicine. Because cellular processes and signaling are influenced by each individual cell's genetic heterogeneity as well as its local microenvironment, biotechnology and hardware systems have evolved to enable more precise interrogation of the cell and probe the central dogma at a *spatial* scale. For example, single-cell sequencing enables the sequencing of DNA or mRNA from an individual cell to discern genetic heterogeneity between cells [14]. Recent advances in *spatial transcriptomics* enables the study of the complex tissue microenvironment at a much greater resolution and at the single-cell level while cells remain in-tact in their native tissue [15].

This brief overview of technology and advances in the multi-omics field exemplifies the importance of such technologies in elucidating underlying cellular mechanisms and signaling pathways towards the discovery of new therapeutics for target diseases. These same technologies are essential for studying the impact of microgravity and the space environment on the human condition and other living systems to meaningfully advance NASA's BPS objectives.

Omics in Space. Numerous studies conducted in a variety of living systems have demonstrated that gene expression is altered in the weightless space environment [16]–[19]. Efforts have been made to develop and implement end-to-end genomics capabilities in space. For example, WetLab-2 was developed as an end-to-end system of methods and tools for collecting, isolating, and purifying RNA for on-orbit sequencing and gene expression analysis [20]. Though the process was successfully demonstrated in orbit, it was not without challenges. The technology and methods have not been developed further due to lack of funding and technical support, although there could still be an opportunity to improve it. Another recent study evaluated the performance of the MinION, a DNA sequencing machine, aboard the ISS and successfully demonstrated the feasibility of sequencing microbial DNA in orbit [21]. Realizing the value of omics research and data, the space science community created the NASA Genelab to be a centralized repository for space omics data [22]. To coordinate efforts between space biologists around omics at a global level, the International Standards for Space Omics Processing (ISSOP) has been established [23]. Interestingly, each of the ten Space Biology research projects selected for funding in 2021 includes some element of space omics [24]. The space science community recognizes the importance of conducting biological research in space in a methodical, controlled, standardized, repeatable manner and has thus outlined the current gaps in a series of recently published peer-reviewed articles [1], [2], [23], [25]. For example, it is important to identify confounding variables and explore methods for either eliminating or controlling for those variables towards achieving meaningful research outcomes. In addition to supporting interesting insights and hypotheses for future research studies, omics data also serve as a tool for quality control and assurance in biomanufacturing of cell and gene therapies where cellular homogeneity is of great importance [26]. Given that microgravity confers an advantage for biomanufacturing (stem cell expansion, organoids, 3D bioprinting) in space based on early space studies, quality control and assurance processes will be essential for successful use of space for biomanufacturing [2]. Finally, synthetic biology holds great potential for the orbital marketplace especially for NASA's deep space exploration goals. For example, a suite of core omics technologies can enable on-demand production of mRNA and proteins, or allow for building living materials, support health and hazard monitoring, aid in food production to name a few applications [27]. Taken together, these activities point to the importance of omics data for biological research in space and are indicative of the space community's keen interest in developing these capabilities further. Thus, while there is great interest in space omics research, state-of-the-art capabilities with streamlined workflows on-orbit are lacking.

Roadmap for advancements in multi-omics in space.

To expertly leverage the unique space environment and conduct complex end-to-end and properly controlled studies in space that lead to meaningful results, innovative insights, and useful applications requires access to and use of the same (or more advanced) state-of-the-art reagents, consumables, hardware, and software tools available on Earth. However, these reagents, consumables, hardware, and software tools and associated methods and protocols must be adapted and validated to function in a weightless space environment because the altered gravity environment may affect the physical and chemical properties of the technology.

Research Questions: To achieve an end-to-end multi-omics workflow adapted for a space-based orbital platform, the following non-exhaustive list of research questions is suggested:

- What are the most important omics workflows for the space research community?
- What are the most broadly applicable omics methods?
- What are the required capabilities for in-orbit sample collection, processing, and data generation for the various multi-omics approaches?
- What are the challenges and opportunities in adapting the terrestrial capabilities for orbital platforms? For example, identify a list of constraints *and* benefits of working in the space environment that must be considered for space-technology development.
- How will the adapted technology affect experimental control protocols? Can the same orbital technology be used terrestrially (which would not only be used for ground controls but also incentivize commercial players with new terrestrial market opportunities)?
- Conduct market research to understand the value of space-based omics for terrestrial commercial players? What is the long-range revenue generation opportunity for developers and suppliers of reagents, consumables, hardware, analytics, etc? Define the value chain of these processes and demonstrate how the commercial players benefit from a space-based market opportunity.

A phased approach can be considered to address these and other research questions:
(a) Request for information (RFI) on understanding the omics landscape for both terrestrial needs and in-space applications
(b) Request for proposal (RFP) for in-space omics technology development
(c) A 10-year commitment to support the in-space omics program

Building new technologies for space-based platforms is costly and requires specific niche expertise. Biotechnology development is an interdisciplinary endeavor that relies on collaborative efforts between the biological and the physical sciences as well as engineers, materials scientists, designers, end-users (in orbit), and business-oriented, market-focused individuals and teams to be successful. This proposal presents an opportunity to use the concept of developing for spaceflight and space platforms as a path to incentivize participation of commercial biotech market leaders in innovating terrestrial technologies for orbital science, which will lead to new market opportunities on the ground, not just off the planet. Furthermore, adopting consistent core omics technologies in space and on the ground will support standardization of protocols which will minimize confounding variables, enable direct comparisons between various experimental conditions, and provide common tools for scientific interrogations across the taxonomy spectrum of life forms with the aim of ultimately developing downstream technologies for a broad range of applications.

A space-omics research campaign that leverages the expertise of leaders and practitioners from a variety of disciplines is essential for successful development, implementation, and adoption of the technologies; for the furthering NASA's exploration goals; and for creating a future space-based market and economy.

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