Build a Space Biology Superhero

Have you ever dreamt to travel beyond the Earth? you have heard so many fascinating space news like astronaut’s space walking, growing plants in International Space Station (ISS), Next Artemis Generation and recent discoveries of James Webb Telescope! And you feel happy while watching space walking in the International Space Station. Isn’t it?

# But the most important question is, do you think, is it easy to live in space then our Earth?

To know the answer, first you should know what are the different between Space and Earth. The most important point always comes in front of our mind is, “Anti-gravity”. Space does not have gravity like Earth, this anti-gravity is known as “Microgravity”. We are safely surviving from radiation on the Earth, because of the Ozone layer. Ozone layer acts like a cover around the Earth and protect from harmful UV radiation. But in the space, there is neither to cover nor protect ourselves. So, how can they survive? On the Earth, we have soil to grow plants and plants can take nutrients from the soil then give us organic molecules – such as starch. But in the space, there is neither soil nor water. So how can astronauts get energy? And plants also need to survive from harmful UV rays. So, how can it possible? More than these, extreme gravity, circadian rhythms will be changed by disrupted sleep, limited food supplies from Earth and personalized treatment. They are the most important difficulties to survive in the space.

By these reasons, astronauts cannot be ready to go far from Earth.

**Is there any solution for this?**

Of course, by using our high technologies, **Biological Superheroes** will help to explore.

# In this article, we will explore

* The environmental stresses of space travel,
* To understand the challenges of space environment,
* To understand how diverse organisms deal with these stresses,
* How scientists are performing biological experimentation in space,
* Biological mission enables in the future mission, and
* Build a “Space Biology Superhero” by combining features from these organisms.

# The environmental stresses of space travel

In 1957, the first living being was launched into space which is the dog whose name was Laika. After this, scientists could study space biology and space medicine and how the organisms show unique biological responses to the space environment.

Especially the two major health hazards are space radiation and microgravity. Solar particle events (SPEs) are produced high-energy protons and heavy ions which are contained in galactic cosmic rays (GCRs) and secondary particles interact with spacecraft shielding. Additionally, microgravity, limited contact with Earth, and physiological and psychological impacts from prolonged isolation in a hostile ecology increase the health dangers from space radiation.

Diagram, schematic

Description automatically generated

Figure 1: The flow of information from the environment in space (Picture was taken from “Cell” Volume 183, Issue 5)

Distance, confinement, hostile/closed habitats, radiation, and microgravity are just a few of the hazards in the space environment presents, and they all have an impact on a variety of organ systems and pose a health risk. Flight tests and ground simulations are improved by keeping an eye on the astronauts and the space environment. These conclusive analyses and experiments result in the creation of countermeasures that are precisely targeted at the risks and health effects of the hazards of the space environment that have been identified. This information flow is a closed loop with feedback at various levels; for instance, models may reveal new risks and models may change because of the application of countermeasures.

## Biological features of spaceflight

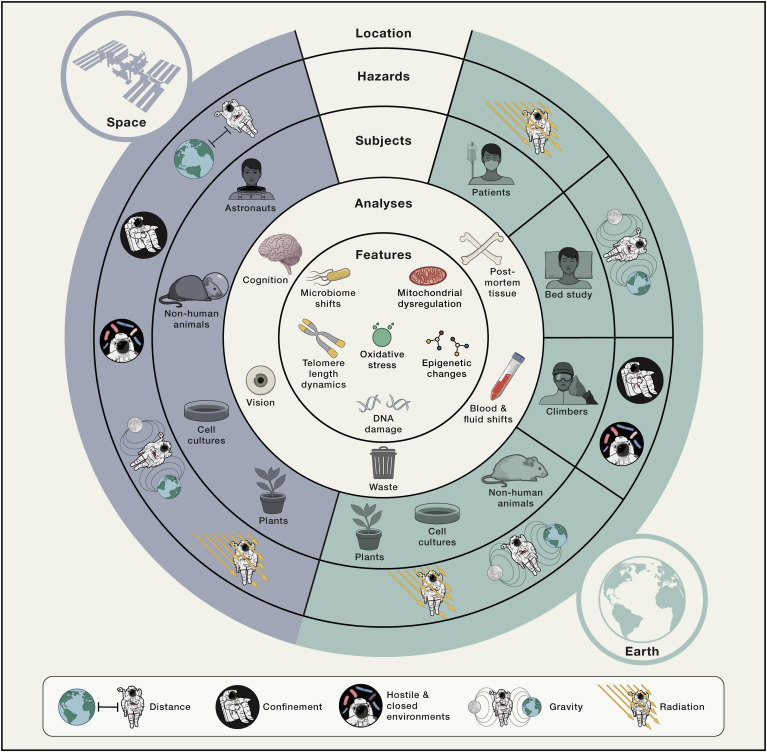


Figure 2: Biological features of Spaceflight (Picture was taken from “Cell” Volume 183, Issue 5)

Health risks and many physiological changes are seen during spaceflight. For instance, bed studies, cancer patients who have received radiation, and climbers help to simulate some of the risks present in the harsh environment of space and offer some insights into how they affect human physiology. Analyses of multiple systems, including cognition, vision, waste, blood, fluid, and post-mortem tissue measurements, are all part of these experiments. These investigations and analyses collectively point to important recurrent molecular and cellular characteristics of spaceflight, such as DNA damage, oxidative stress, mitochondrial dysregulation, microbiome shifts, epigenetics changes, and telomere length dynamics. These characteristics assist in explaining the mechanisms behind some of the systemic and physiological effects of spaceflight.

Space radiation

In deep space mission, ionizing radiation is a major health risk. The energetic solar particles released during solar flares and coronal mass ejections as well as galactic cosmic rays, which are made up of protons (85%), helium nuclei (12%), and heavier ions known as high-energy and high-charge particles (HZE; 1%), are all included in the space-radiation environment. According to Cucinotta and Durante (2006), astronauts on the ISS receive an average dose of 100-200 milliSieverts (mSv) of radiation per year, whereas the annual exposure limit for professionals who work with radiation is 50 mSv/year. According to Zeitlin et al (2013) and Iosim et al (2019), future missions to Mars will receive doses that are even higher, up to 350 mSv/year for a mission of about three years, and they will primarily be made up of highly biologically active galactic cosmic rays.

Microgravity

Gravity is a vector on the Earth. In the environment of space, gravity is removed mostly, and results is microgravity conditions. Additionally, there are frequently strong forces encountered during exit and descent transitions through atmospheres, which are frequently stronger than the force of gravity, stressing biological systems. The genome, epigenome, and proteome are all altered by microgravity, and these modifications increase the risk of developing a variety of pathologies. The biological mechanisms that have developed to react to gravity can cause abnormal physiological reactions in microgravity at the organismal level. For instance, fluids, including blood, move upward toward the head and thorax, resulting in a reduction in the volume of the legs and compensatory changes to the cardiovascular system. Furthermore, since there is no longer any gravitational loading on bones and muscles, they atrophy through remodeling processes, the molecular mechanisms of which are still poorly understood. Additionally, prolonged microgravity’s synergistic effects in addition to other risks associated with the space environment could exacerbate complex health issues in astronauts preparing for length missions.

Confinement and isolation

Astronauts will spend a lot of time confined and alone in a small spacecraft during deep space travel. Risks to psychological, behavioral, and physiological health are likely to rise with increased physical and social isolation and unprecedented distance from Earth. On Earth, social isolation has been investigated using analog environments on human subjects as well as animal models, showing that it may result in neurological deficits, including impaired hippocampal functions. Additionally, isolation may directly contribute to immune dysregulation based on human results from analog missions in the Arctic. Findings in animal models exposed to simulated microgravity combined with social isolation suggest that social isolation combined with other spaceflight hazards could worsen outcomes (Tahimic et al., 2019).

Hostile and closed environment

Astronaut Continuous and prolonged habitation in an enclosed spacecraft ecosystem presents a biologically hostile and closed environment for astronaut health. Spacecraft habitability must be monitored for temperature, air quality, microbial inhabitants, pressure, lighting, and noise to help ensure effective countermeasures for a healthy environment. Constant noise, high carbon-dioxide levels, and limited microorganism ecosystems together might affect cardiovascular, neurological, and immune health. For example, levels of ambient noise have been demonstrated to contribute to cardiovascular impairments, sleep disturbance, and cognitive deficits (Münzel et al., 2020). In addition, due to limited efficacy of air recycling systems, increased CO2 is a common feature on spacecraft and can lead to a hypoxic/hypercapnic response (Beheshti et al., 2018). Finally, prolonged confinement is likely to reduce the variability of the environmental microbiome, which might adversely affect astronaut immune functions and metabolism (Voorhies and Lorenzi, 2016).

Distance from Earth

Distance from Earth itself, the final significant spaceflight hazard, results in psychological stress and disturbs team dynamics. Due to communication lags, the lack of rapid evacuation or immediate rescue during missions beyond low earth orbit, and other equipment limitations, distance from Earth will also limit medical treatment options and capabilities. Therefore, there is a gap in the market for autonomous health support for flight medical officers. This support could come in the form of surgical interventions advancements in wearable sensors and health monitoring, AI-assisted medical diagnostics, on-board genetics and sequencing capacity and health-risk prediction.

# Challenges of the Space Environment

Six feature of biology characters guide the understanding of fundamental molecular changes during space travel. Such as, oxidative stress, DNA damage, mitochondrial dysregulation, epigenetic changes, telomere length alteration and microbiome shifts.

### oxidative stress

Elevated oxidative stress is the first characteristic of spaceflight biology, and it is one of the primary responses to the conditions of spaceflight that can result in DNA damage. When a cell's natural antioxidant capacity is exceeded by the amount of free radicals present, oxidative stress results. Reactive oxygen and nitrogen species (ROS, RNS) are produced by cells in response to exposure to radiation from space, hypoxia, and microgravity. This effect was observed in 13 astronauts on long-duration (>4 months) ISS missions as well as in 59 astronauts' urine levels of 8-oxo-guanosine. A linear energy transfer (LET)-dependent oxidative stress response has also been noticed in human immune cells ex vivo, focusing on radiation-induced oxidative damage. Dysregulations of the cardiovascular, immune, neurological, and metabolic systems are brought on by spaceflight at the physiological level by oxidative stress and an imbalance in the oxidation-reduction system.

### DNA damage

Ionizing radiation damages DNA by inducing DNA breaks through direct or indirect radiolysis interactions with the DNA molecule. Excision repair mechanisms make it simple to fix single-strand breaks, but double-strand breaks (DSBs) require more involved repair procedures. Risks of mis repair can result in cell-cycle arrest, cell death, mutations, chromosomal rearrangements, and subsequent carcinogenesis.

Unlike low-LET radiation, HZE particles deliver elevated local doses to the cell nucleus by traveling through thousands of cells and depositing their energy along densely ionizing tracks (Magee and Chatterjee, 1980). High relative biological effectiveness (RBE) for carcinogenesis is caused by this unique energy-deposition pattern, especially for high-LET GCR components like 12C, 20Ne, 28Si, 48Ti, and 56Fe (Cacao et al., 2016). In fact, DSBs caused by HZE particles group together to form radiation-induced foci (RIF) and heal more slowly than do DSBs caused by low-LET radiation individually. A single RIF may contain multiple breaks, making its interpretation complicated and requiring consideration of the labeled protein's function, the capacity of damage recognition, the effectiveness of repair, and the complexity of the damage.

Based on directional genomic hybridization, which found an increase in intra-chromosomal inversions during and after spaceflight, DNA damage was recently shown for the first time in astronauts. This finding may be related to stem-cell damage, clonal hematopoiesis, and/or instability (Garrett-Bakelman et al., 2019; Luxton et al., 2020a, 2020b; Trinchant et al., 2020). Extremely radio tolerant organisms like the tardigrade have been studied, and it has been discovered that they have a special damage suppressor protein that may help prevent DNA damage brought on by repeated exposure to space radiation (Westover et al., 2020 [unpublished data]).

### Mitochondrial dysregulation

A decrease in the expression of mitochondrial oxidative phosphorylation (OXPHOS) genes encoded by nuclear DNA and a significant compensatory induction of OXPHOS genes encoded by mitochondrial DNA (mtDNA) are both signs of dysfunctional mitochondria. Recent studies have revealed that astronauts' mitochondrial OXPHOS and related fatty-acid oxidation are impaired, which is consistent with their higher systemic lipid levels. Additional evidence from mice sent into space has also demonstrated that liver function directly controls levels of lipids and carbohydrates. Therefore, modifications in liver function and substrate levels caused by modifications in systemic mitochondrial function should also affect substrate levels. Increased mitochondrial ROS production linked to higher levels of 8-hydroxy-deoxyguanosine (a byproduct of DNA oxidation) and prostaglandins, decreased antioxidant defense mechanisms, and altered circadian rhythms with reduced NAD+/NADH ratios impairing Sirt1 deacetylation of BMAL are additional signs of mitochondrial impairment in astronauts (Nakahata et al., 2008). In fact, a multi-omic analysis of human and mouse responses to spaceflight has shown that mitochondrial dysregulation is one of the most significant physiological alterations (da Silveira et al., 2020).

Since mitochondria take up a lot of cellular space and are frequently affected by radiation, ionizing radiation also causes ROS to be produced there (Leach et al., 2001). Ionizing radiation amplifies mitochondrial ROS, which causes mutations in the mitochondrial DNA and disrupts the expression of crucial proteins for mitochondrial and cellular functions (Azzam et al., 2012). Notably, oxidative damage in mitochondrial DNA (mtDNA) is several times higher than in nuclear DNA (Richter, 1992), which may be related to the fact that mtDNA lacks protective histone proteins and that its DNA repair mechanisms are less effective (Wiseman and Halliwell, 1996).

### Epigenetic and gene regulation changes

Scott Kelly's year-long mission revealed numerous epigenetic and gene-expression changes, but most of them returned to normal upon his return to Earth, and some sites showed even less change than the ground control (his twin brother Mark Kelly, during the same amount of time). For instance, even after a year in space, Scott's overall DNA methylation landscape was less divergent than Mark's. This suggests that a strict, dependable schedule for eating, sleeping, exercising, and interacting with the environment on the ISS might prevent epigenetic changes. However, other studies on chromatin landscapes from sorted cells and single-cell sequencing have revealed notable variations in chromatin accessibility and epitope levels prior to and following spaceflight.

The accessibility of DNA repair proteins (Chiolo et al., 2011) and homology search during repair (Miné-Hattab and Rothstein, 2012) are particularly improved by chromatin de-condensation following DSB induction (Krawczyk et al., 2012). As a result, chromatin de-condensation promotes gene transcription and is a key mechanism of radiation-induced epigenetics (Handy et al., 2011). In addition to DSBs, ROS were demonstrated to directly influence chromatin condensation (Coluzzi et al., 2019), suggesting that oxidative stress brought on by radiation and microgravity (Adrian et al., 2013) could result in epigenetic modifications via chromatin relaxation.

### Telomere-length dynamics

Telomeres, tandem arrays of repetitive G-rich sequences and associated proteins, cap the ends of human chromosomes and serve to prevent chromosomal termini from deteriorating. By preventing natural chromosomal ends from being identified as DSBs and from inducing unneeded DNA damage repairs, telomeres also protect genome stability (DDRs). The "end-replication problem" causes telomere length to shorten with cell division and aging as a result. Along with numerous other lifestyle factors like stress (such as dietary, physical, and psychological strain), environmental exposures, infections, and inflammation, oxidative stress, infection, and inflammation all contribute to the shortening of telomeres (e.g., air pollution, radiation). Because they may reflect the sum of exposures and experiences had while living in the harsh environment of space, telomere-length dynamics (changes over time) represent a pertinent and integrative biomarker for astronauts. Furthermore, because altered telomere length is associated with age-related pathologies like dementia, cardiovascular disease, and cancer, all of which have the potential to affect astronaut health and performance during and after long-duration missions, longitudinal analysis of telomere length offers an informative indicator of general health, aging, and aging trajectories.

By analyzing telomere-length dynamics and genome stability in space-bound and Earth-bound twins Scott and Mark Kelly, the issue of aging brought on by long-duration spaceflight was addressed for the first time in astronauts (Garrett-Bakelman et al., 2019). Blood samples from a cohort of ten unrelated astronauts and age- and sex-matched ground control subjects were taken before, during, and after spaceflight in related studies (Luxton et al., 2020a). For all crew members for whom in-flight samples were available, regardless of mission duration, sample type, or method of measurement, telomere elongation during spaceflight was the most startling finding (Luxton et al., 2020b). Telomere length also decreased rapidly after returning to Earth, and crew members had significantly more short telomeres than they had before their spaceflight. Chronic space radiation exposure and its closely related DDRs, along with several stress reactions, may influence telomerase-dependent and/or independent telomere maintenance pathways (Bezdan et al., 2020; da Silveira et al., 2020; Grigorev et al., 2020 [unpublished data]; Luxton et al., 2020a, 2020b; Trinchant et al., 2020). Results emphasize the significance of monitoring each crewmember's telomere length and genome stability as a means of evaluating general health, disease, and aging risk; information that should then be considered for development of personalized aerospace medicine and countermeasures for future astronauts. Although definitive mechanisms and temporal health effects of such dramatic, spaceflight-associated shifts in telomere-length dynamics are yet to be determined, results highlight the importance of monitoring individual crewmember telomere length and genome stability.

### Microbiome shifts

The microbiome is a constantly shifting ecosystem of microorganisms that live inside of humans, and all-around environment. In spaceflight biology, the microbiome can be divided into two main parts. The astronauts' own microbiomes, which include the oral, skin, and other specialized bodily microbiomes, can change first. The Firmicutes to Bacteroidetes (F/B) ratio shifted in the NASA Twins study, but the overall diversity of the gut microbiome was preserved (Garrett-Bakelman et al., 2019). Additionally, the richness and diversity of the gut microbiome increased steadily or significantly in astronauts on six to twelve-month missions (Voorhies et al., 2019). Despite these preliminary studies, there is still much that is not fully understood about how spaceflight affects microbiome dynamics and how this affects human health (Voorhies et al., 2019), including changes to the microbiome of the saliva and the reactivation of viruses like the herpes virus (Urbaniak et al., 2020).

The microbiome of the spacecraft environment is the second element. Shotgun metagenome sequencing of the ISS environment has identified the existence of healthy microbial communities and revealed sporadic increases in virulence gene factors and antimicrobial resistance (Singh et al., 2018). The microbial composition of ISS environmental surfaces was different from that of Earth analogs, according to a comparison of the two systems' microbial compositions (Lang et al., 2017a; Singh et al., 2018). Additionally, research has revealed that the skin microbiome of the crew is most like the ISS environmental microbiome (Avila-Herrera et al., 2020). Several hundred strains of the environmental surface samples from the ISS have had their entire genomes sequenced, and this has resulted in the discovery of novel species. These include the *Bacillus creus-anthracis* clade, *Kalamiella piersonii*, and *Solibacillus kalamii* (Checinska Sielaff et al., 2017).

# How diverse organisms deal with these stresses

The risks to the astronauts' health during their mission as well as their long-term health afterward define the health risks, which affect many different organ systems. Cardiovascular system, central nervous system, increased cancer risks, the musculoskeletal system, immune system, gastrointestinal system, dysregulation of the circadian system and vision changes are major health risks.

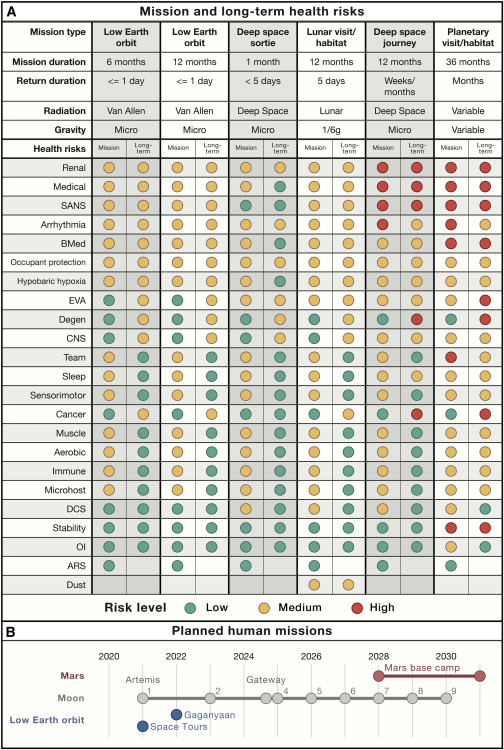


Figure 3: A. Astronaut Mission and Long-Term Health Risks

Depending on the type of mission, mission-specific and long-term health risks are listed. LEO, deep-space sortie, lunar visits, deep-space travel, and planetary visits are among the mission types. These missions can be identified by their characteristics, which include gravity, radiation exposure, mission duration, and return duration. To indicate the NASA-defined overall safety risk scores (low to high, green to red, respectively) for mission risk and long-term risk, astronaut health risks spanning multiple organ systems are included.

Arrhythmia, risk of cardiac rhythm issues; ARS, risk of acute radiation syndromes due to SPEs; Aerobic, risk of decreased physical performance due to decreased aerobic capacity; Cancer, risk of radiation carcinogenesis; BMed, risk of detrimental cognitive or behavioral conditions and psychiatric disorders; Risk of immediate (in-flight) and long-term effects of radiation exposure on the central nervous system; Decompression sickness risk, or DCS; cardiovascular disease risk, other tissue degenerative effects brought on by radiation exposure, and additional stressors associated with spaceflight; dust, the possibility of negative effects on one's health and ability to perform; EVA, injury risk, and performance issues brought on by EVA operations; risk of crew members' health and performance being negatively impacted by hypobaric hypoxia; immune, risk of negative health outcomes and performance declines due to in-flight medical conditions; medical, risk of negative health outcomes and performance declines due to altered immune response; risk of negative health effects from host-microorganism interactions in the microhost; muscle, the possibility of performance being hampered by a loss of muscle mass, strength, and endurance; occupant safety and potential harm from dynamic loads; OI, the potential for orthostatic intolerance when returning to gravity; renal, the potential for kidney stones; Spaceflight-Associated Neuro-Ocular Syndrome (SANS) risk vestibular/sensorimotor changes brought on by spaceflight pose a risk of impaired spacecraft/associated systems control and reduced mobility; stability, risk of toxic or ineffective medications due to long-term storage; sleep, risk of performance declines and negative health effects caused by sleep loss, circadian desynchronization, and work overload; risk of performance and mental health declines as a result of insufficient teamwork, coordination, communication, and psychosocial adaptation.

B. Over the following ten years, until 2030, human missions to LEO, the Moon, and Mars are planned. ISS missions are scheduled for every year in low-earth orbit.

### Cardiovascular dysregulation

When in space, the cardiovascular system is not subjected to gravity's normal loading effects, which leads to "aging-like" deconditioning, such as a decline in physical fitness, arterial stiffening, and the emergence of insulin resistance. Reduced circulatory blood volume, lower arterial blood diastolic pressure, smaller left ventricles, post-flight orthostatic intolerance, and decreased cardiac contractility are some of the acute effects on cardiovascular physiology (Patel, 2020; Walls et al., 2020 [unpublished data]). Along with DNA damage and oxidative stress, space radiation amplifies the effects of microgravity as seen in the heart and vasculature (Patel, 2020; Bishawi et al., 2020 [unpublished data])

After flights, orthostatic intolerance frequently occurs, causing syncope and tachycardia in many astronauts (Buckey et al., 1996). According to Soucy et al. (2011) and Yu et al. (2011), space radiation in mouse models results in aortic stiffness, accelerated atherosclerosis, increased DNA oxidation, myocardial fibrosis, and altered cardiac function (Yan et al., 2014). Small vessels also react to radiation from space: hippocampal microvasculature is lost after exposure to iron ions (Mao et al., 2010), and heavy ions similarly cause micro-vessels to collapse in human 3D micro-vessel models (Grabham et al., 2011; Malkani et al., 2020).

In addition, depending on whether the radiation is made up of light or heavy ions, space radiation inhibits angiogenesis in human micro-vessel models through two different mechanisms (Grabham et al., 2013). Although they also work in concert, light and heavy ions primarily prevent the later stages of micro vessel development while inhibiting the early motile stages (Wuu et al., 2020). Inhibiting angiogenesis in small blood vessels results in a gradual loss of vessels because damaged vasculature is not replaced, which causes rarefaction and pathologies in the deprived tissues (Vernice et al., 2020). Rarefaction eventually results in limb pain, high blood pressure, a sustained rise in the risk of hypertension, arterial thromboembolism, cardiac ischemia, and cardiac dysfunction on an organismal level (Abdel-Qadir et al., 2017). The central nervous system's (CNS) micro-vessels may also be a factor in the CNS impairments because the space environment harms them as well.

### CNS Impairments

Future missions are warned that prolonged GCR exposure outside of Earth's magnetic field poses a serious risk to their health (Figure 3A). Models of GCR neurotoxicity based on rodent ground simulations currently available (Simonsen et al., 2020). According to Krukowski et al. (2018), these simulated GCRs and their most biologically active byproducts, HZE particles, cause cognitive and behavioral deficits associated with neuroinflammation and neuronal damage (Parihar et al., 2018). Following GCR irradiation, these physiological and behavioral changes persist for a considerable amount of time, raising the possibility of additional neurological harm during post-flight re-acclimation to ground conditions.

In rodents and other model organisms, GCR irradiation, simulated microgravity, and spaceflight all have similar effects on the central nervous system (CNS), including behavioral deficits and oxidative stress at the cellular-tissue level (Santucci et al., 2012). Therefore, it is possible to anticipate that multiple spaceflight stressors will exacerbate CNS damage during deep space missions. This was recently demonstrated by executive function impairments brought on by prolonged neutron exposure and made worse by fragmented sleep.

According to animal models, CNS reactions to spaceflight and simulated GCR exposure resemble a number of terrestrial diseases, such as normal neurological aging and neurodegeneration (Clément et al., 2020). GCR exposure may therefore make age-related brain damage worse. However, the mechanistic parallels between space travel and neurological disorders encourage the use of recently developed computational tools for drug repurposing (Nelson et al., 2019) to identify novel therapeutic targets and FDA-approved inhibitors.

It is anticipated that CNS impairments will coexist with spaceflight's systemic effects, such as immune dysfunction (Mehta et al., 2017), which could exacerbate neuroinflammation by crossing the blood-brain barrier. The finding that the peripheral immune phenotype can act as a biomarker for behavioral deficits after HZE particle irradiation supports the relationship between the CNS and systemic immunity (Krukowski et al., 2018). Therefore, it will be crucial to consider the blood-brain barrier as both a target of CNS damage and as a potential location for delivering systemically applied countermeasures into the brain (Bellone et al., 2016). (Kariolis et al., 2020).

### Increased cancer risks

One of the major hazards associated with deep space exploration is radiation-induced cancer, and space agencies all over the world have established career dose caps based on the anticipated cancer risk. A dose of 1 Sv is associated with a 5% increased risk of dying from cancer, so NASA has set the career limit for a 25-year-old female at 1 Sv, ranging up to 4 Sv for a 55-year-old male. There is no equivalent on Earth to assess the cancer risk from GCR components, except for secondary tumors brought on by particle-based radiotherapy. Although photons and HZE particles have a different energy deposition pattern, epidemiological studies of atomic bomb survivors exposed to acute doses of low-LET radiation have been scaled to predict cancer risk from high-LET radiation using the RBE concept (Costes et al., 2006).

Since radiation-induced cancer incidence in rodents and humans is similar (Storer et al., 1988), simulations of GCR components on Earth have been applied to rodent models extensively. These simulations show higher induction of some tumors compared to models of low-LET radiation (Cucinotta et al., 2013). High RBE of HZE particles have specifically been linked to the development of mammary tumors, Harderian gland tumors, skin tumors, intestinal colorectal cancer, leukemogenesis, and hepatocellular carcinoma (Illa-Bochaca et al., 2014; Kennedy et al., 2008; Burns et al., 2007). (Weil et al., 2014). On the other hand, HZE ions are not any more effective than gamma rays at causing ovarian cancer (Watanabe et al., 1998) and acute myeloid leukemia (Weil et al., 2014), which may suggest different underlying mechanisms for causing these tumor types. Importantly, in contrast to spontaneous and low-LET-induced tumors, no novel tumor types have been seen in rodents exposed to HZE ions (Bielefeldt-Ohmann et al., 2012). Given the current discrepancies, more information is needed to better understand how dose fractionation affects carcinogenesis (Bielefeldt-Ohmann et al., 2012).

Most computational models of the interactions between GCR particles and biological targets have been used to predict cancer risk in humans (Cucinotta et al., 2013). In order to account for inter-individual variations, human responses to GCR components have recently undergone in vitro evaluation in a significant cohort of 600+ healthy donors (Pariset et al., 2020 [unpublished data]). In order to improve cancer risk predictions, new 3D tissue models (Low and Giulianotti, 2019) and thorough systems biology analyses (Barcellos-Hoff, 2008) will add new information on how people react in actual spaceflight conditions.

### Muscle degeneration

Microgravity exposure results in a loss of performance, volume, and muscle mass. On both short- and long-haul flights, this effect is most noticeable in the legs (Fitts et al., 2000). Like bone, regional variations in muscle loss appear to depend on each region's function in battling gravity; however, while the neck's muscles are not significantly impacted, the lower extremities are (McNamara et al., 2019). Inflammatory markers driving muscle and bone metabolism were discovered through biochemical profiling of astronauts before, during, and after spaceflight, demonstrating the negative effects of microgravity while in space as well as the effects of returning to gravity (Gertz et al., 2020).

Losing muscle in space, whether through actual flight or ground-based simulations, is similar to a catabolic patient experiencing metabolic breakdown. This is a crucial and perplexing problem because insufficient energy intake will result in the same outcomes. The question of whether spaceflight in and of itself causes loss of muscle mass and performance, or whether these findings are confounded by inadequate dietary intake, still remains given that many, if not the vast majority of astronauts don't meet energy intake requirements and lose body mass. Energy intake and metabolic breakdown are closely related to mitochondrial biogenesis, and it has been suggested that mitochondrial dysfunction is a key factor in this process.

Exercise is the most obvious preventative measure for cardiovascular, bone, and muscle health (Lang et al., 2017b). However, on Russian space station Mir flights, crew members varied greatly in terms of the frequency and intensity of in-flight exercise, and loss of leg muscle volume was close to 20% in all subjects (LeBlanc et al., 1996). In 2008, the Advanced Resistance Exercise Device (ARED) and a second-generation treadmill were launched to the International Space Station (ISS), and they were successful in boosting lean body mass (Smith et al., 2012; Smith et al., 2014).

### Bone loss

The risk of developing renal stones during the mission and an increased risk of bone fracture after flight are just two of the numerous risks associated with bone loss during spaceflight (Smith et al., 2015b; Sibonga et al., 2020). Weight-bearing bones account for most of the bone loss experienced during spaceflight, which results in a monthly loss of total bone density of between 1% and 1.5%. This is comparable to the amount of bone a postmenopausal woman on Earth loses over the course of a year. According to Sibonga et al. (2017), an important aspect of spaceflight-induced bone loss is individual variability, which may offer insight into ways to slow this loss. In other words, it is possible to assess astronauts to find out what they did differently that resulted in them losing more (or less) bone than other astronauts (e.g., exercise, diet).

Bone is a metabolically active tissue that constantly undergoes formation and breakdown (resorption). Despite exercise countermeasures, spaceflight increases bone resorption, which is primarily measured by excretion of collagen crosslinks (Smith et al., 2005; Smith et al., 2015b). Without effective exercise-induced bone loading, bone formation, on the other hand, is typically unchanged or decreased during spaceflight (Smith et al., 2005). During spaceflight, increased levels of bone resorption and decreased or unchanged levels of bone formation result in an overall calcium balance that is negative, which causes bone loss and an increased risk of kidney stones.

The ability of astronauts to maintain bone mineral density has been made possible by resistance training using the ARED on board the International Space Station (Smith et al., 2012; Smith et al., 2014), but there are still questions and concerns about bone architecture, turnover, the effects of qualitative strength, and drug therapeutics (Leblanc et al., 2013). Numerous nutrients have been investigated for their potential to slow bone loss, including calcium, omega-3 fatty acids, sodium, protein, potassium, and vitamin K (Zorbas et al., 2008). (Smith et al., 2015b). There is evidence linking radiation, oxidative stress, and bone health (Tian et al., 2017).

### Immune dysfunction

Astronauts experience a complex pattern of immune dysfunction as a result of spaceflight (Figure 3A). Reduced T and NK cell activity, modifications to the monocyte and granulocyte pattern-recognition systems, and adjustments to cytokine levels are the main components of this dysfunction. These result in a shift in the Th1/Th2 cytokine balance toward Th2-cell mediated immunity and a mild persistent inflammatory response, which together cause the subclinical reactivation of dormant herpesviruses (Crucian et al., 2014b; Mehta et al., 2017; Ponomarev et al., 2017). Atopic dermatitis, atypical allergies, and mild infectious diseases are examples of negative clinical events that may affect some crew members (Crucian et al., 2016). Animal models of spaceflight and ground analogs, astronaut blood (Barrila et al., 2016), and space-flown mouse splenocytes have all shown signs of a similar type of immune dysfunction (Baqai et al., 2009). Mechanical forces can modulate the stimulus response thresholds of human T cells, according to data from spaceflight and ground simulation studies (Hauschild et al., 2014). This finding could help to partially explain the effects of spaceflight.

Additionally, mild chronic systemic inflammation can be brought on by spaceflight, post-flight reacclimation to Earth, and simulated deep-space radiation. The Twins Study (Garrett-Bakelman et al., 2019) reported transcriptomic signatures associated with inflammation, which are consistent with slight increases in inflammatory cytokine levels from other studies on astronaut plasma (Crucian et al., 2014b; Gertz et al., 2020). In a similar vein, simulated GCR impairs immune responses in animal models, increasing cardiovascular inflammation and neuroinflammation with related neuronal damage (Boerma et al., 2015). (Acharya et al., 2019; Krukowski et al., 2018).

Notably, ongoing immune research from the time the International Space Station was built until the present suggests that more recent orbital crews may have had improved immune status (Crucian et al., 2020), which has been attributed to the implementation onboard the ISS of specific behavioral, exercise, and dietary countermeasures. The countermeasure protocol, which includes dietary supplements, a particular exercise regimen, stress-relieving methods, and pharmacological interventions, was recently published by an international team. It is designed to keep immune competence during deep-space missions (Makedonas et al., 2019). Based on the similarities between autoimmune disorders, immune deficiencies, and spaceflight-mediated immune dysfunction (Crucian et al., 2014b; Mehta et al., 2017), additional defenses might be developed, opening the door to drug repurposing for use in spaceflight.

### Increased liver disease and lipid dysregulation

Recent evidence has started to mount highlighting significant liver-related changes brought on by spaceflight. Animal livers used as ISS, shuttle, and microgravity ground models all showed damage that contributed to an increase in the processing of lipid and fatty acids (Beheshti et al., 2019; Jonscher et al., 2016). Fibrosis and non-alcoholic fatty liver disease could result from these modifications (NAFLD). According to da Silveira et al. (2020), elevated levels of cholesterol (low- and high-density lipoprotein) were observed in astronauts throughout their 180-day space mission, with levels continuing to be elevated up to 30 days after their return to Earth.

### Circadian rhythm dysregulation

Disrupted cycles of light and dark are one distinctive feature of the enclosed and confined spacecraft environment. For instance, the ISS has a 90-minute sunrise-to-sunset interval. Additionally, periods of high activity on board a spacecraft (also known as "slam shifts" such as those surrounding launch, docking, and spacewalks) may subject crew members to the equivalent of shift work and prevent them from getting enough sleep. Circadian rhythms are present in a variety of processes, including molecular (e.g., gene expression), systemic (e.g., cortisol levels), and behavioral (e.g., mood). All of these processes tend to be influenced by the cycle of light and darkness but may be disturbed by non-24-hour periodicity or the presence of conflicting signals.

Different model organisms have shown spatial variations in circadian rhythm. Drosophila melanogaster has been used to study how circadian rhythms and gene expression are affected by space travel (Ma et al., 2015). Non-human primates on Cosmos missions (Fuller et al., 1996) and rats on Neurolab missions have both experienced changes in body temperature rhythm that are related to space (Fuller et al., 2003). Rodent spaceflight samples have shown altered expression of circadian-associated genes and pathways, including liver tissues and skeletal muscle (Allen et al., 2009). (Beheshti et al., 2019). Last but not least, changes in circadian behavioral rhythms have been observed in astronauts, other astronauts, and shift-working flight controllers on Earth (Garrett-Bakelman et al., 2019; Flynn-Evans et al., 2016). (Mizuno et al., 2016).

However, single time point samples cannot distinguish between differences in circadian phase, misalignment, reduction of amplitude, or other disruptions to the circadian system because a sizable portion of proteins or transcripts in a given tissue may exhibit diurnal or circadian changes (Zhang et al., 2014a) (Braun et al., 2018). Data interpretation is constrained due to a lack of information regarding sleep-wake patterns at the time of sample collection (Skene et al., 2018). To fully comprehend the nature of the effects of spaceflight on circadian rhythms, more research with model organisms is required, including comparisons of samples taken at various times of the day or longitudinal samples (such as the Twins Study).

Circadian rhythms are widely acknowledged to have an impact on a variety of health issues, many of which are relevant to space travel (Figure 3A). Circadian disruption has been linked to impairments in bone health, metabolism, mitochondrial function, inflammation, and immune system function (Song et al., 2018; Panda, 2016). (Gachon et al., 2018). Additionally, gastrointestinal function depends on sleep and circadian rhythm. The normal gut microbiome can be altered by both sleep and artificially induced circadian rhythm disturbances (Deaver et al., 2018). The gut microbiome also has its own circadian or diurnal rhythms. Circadian rhythms may be a common factor linking many of the characteristics of spaceflight biology to health risks because of the circadian clock system's role in the temporal coordination of nuclear, mitochondrial, cellular, and systemic processes.

### Space-associated neuro-ocular syndrome

Almost instantly after exposure to spaceflight, fluids move from the lower to upper body (Thornton and Rummel, 1977). According to Norsk et al. (2015), increased cardiac output and gastrointestinal function can both be affected by the headward shift of about 2 L of fluid (Lane et al., 1993). These impede the perception of tastes and odors by the special senses and may be a contributing factor in space-associated neuro-ocular syndrome (SANS).

Optic disc edema, choroidal and retinal folds, flattening of the posterior sclera, and hyperopic refractive error shifts are all signs of SANS (Lee et al., 2020). There are several published theories, some of which suggest an involvement of a cephalad fluid shift, though the precise mechanism is not yet fully understood.

Although it has been hypothesized that increased intracranial pressure (ICP) contributes to SANS, there is currently no evidence to support this theory, and astronauts typically report few or no symptoms (such as headaches) related to increased ICP (Laurie et al., 2020; Lawley et al., 2017). However, cases of optic disc edema have been documented in both spaceflight and strict head-down tilt bed rest (Laurie et al., 2020), and altered one-carbon metabolism has been linked to ocular changes in both of these models (Zwart et al., 2019). Recent research suggests that oxidative stress and mitochondrial dysfunction are some of the biological factors that may contribute to SANS (da Silveira et al., 2020).

Given that SANS is more common in men and that not all crew members who have flown long-duration missions experience it, the cause is probably complex (Laurie et al., 2020). For instance, due to genomic variations, the effects of a cephalad fluid shift may vary between crewmembers (Zwart et al., 2016; Garret-Bakelman et al., 2019). Endothelial dysfunction may result in leakier vessels and edema due to genetic differences in one-carbon metabolism in combination with other factors like fluid shifts, radiation exposure, CO2, a higher body mass index, or a diet low in B vitamins (Smith and Zwart, 2018). To fully understand how much these genomic and environmental factors contribute to the development of SANS, however, more research is required.

# How are scientists performing biological experimentation in space?

Studying cells grown in the microgravity environment, or "weightlessness," of the International Space Station can teach biologists a lot about how life functions differently in space and how this affects human health. With the help of the Bio culture System, a brand-new research facility for the orbiting laboratory, scientists will be able to conduct extensive cell biology studies on a variety of topics and different cell and tissue types. With the help of this new hardware, cell cultures can be remotely monitored in real-time, and their growth conditions can be managed more precisely. Cell Science Validation, the system's first mission, will thoroughly test the system's intricate engineering and life support capabilities to ensure that it can operate as intended in microgravity and successfully grow a variety of cells on the space station, including bone and heart cells in this experiment. The facility will be made available to the entire scientific community for exciting, new, cutting-edge research after the initial validation is finished, including fundamental cell biology, drug discovery, microbiology, and tissue engineering. Patients with long-term immobility due to injuries, cancer, aging, or other conditions frequently experience muscle wasting. Even in microgravity, astronauts experience muscle atrophy. To prevent muscle wasting and the need for daily or frequent drug administration, the Rodent Research-6 study will assess a novel drug delivery system that delivers continuous, low doses of medication. Through a silicone membrane with channels as small as 1/50,000 the width of a human hair, a tiny capsule implanted under the skin administers a consistent, low dose of the medication. The low-dose administration may also help prevent the known side effects of long-term use of high doses. Formoterol is a medication that is frequently used as a treatment for lung conditions such as asthma. It releases the muscles that are causing a patient's airways to constrict. When released by a tiny, but potentially strong device, Rodent Research-6 will examine how well it can prevent muscle wasting. Gravity is a constant stimulus for plants, which use it to send shoots up and roots down as well as to shape their overall shape. The mission to understand how much gravity a plant seedling can sense is called "Plant Gravity Perception." The experiment will use a centrifuge system to simulate various levels of gravity while operating in the space station's microgravity environment. To determine whether there is a threshold level that plants must reach in order to sense gravity, respond, and thrive, video data of the plants' reactions will be collected. Understanding how this operates could aid scientists in creating plants that are hardier for use in agriculture on Earth or that are well suited for growth on lengthy space missions. These are the same kinds of microorganisms that exist on Earth and would have been transported to the space station initially on supplies or on astronauts during crew changes. Researchers need to know what kinds of microorganisms may already be present on the space station in order to catalog and characterize potential disease-causing microbes. Before, during, and after the astronauts' flights, samples are taken from their bodies. Additionally, surface and air locations near the station are sampled for environmental factors. The samples are examined for potential microbe types and to determine whether any could have an impact on human health. Both the emergence of microbial communities and interactions between the microbes are investigated. SpaceX resupply missions have already delivered microbial sampling kits and returned earlier samples to Earth for scientific analysis. Researchers can observe how the microbial population on the space station is changing by taking numerous samples over time. The outcomes of this study may contribute to understanding how microbes impact the health of the crew and the effectiveness of the spacecraft. With this knowledge, NASA can create strategies to reduce the impact of microorganisms on lengthy space missions manned by explorers.

# Biological mission enables in the future mission

The limits of gravity have always guided the evolution of life on Earth. In space, organisms experience entirely new circumstances like radiation and weightlessness. Most space experiments to date have shown that microgravity significantly affects the growth and behavior of organisms. The exploration of how microgravity affects living systems at the cellular and molecular levels, as well as the genetic stability, growth, and development of animal and plant systems, should be the primary objectives of future space and gravitational biology research programs. The limits of gravity have always guided the evolution of life on Earth. In space, organisms experience entirely new circumstances like radiation and weightlessness. Most space experiments to date have shown that microgravity significantly affects the growth and behavior of organisms. The exploration of how microgravity affects living systems at the cellular and molecular levels, as well as the genetic stability, growth, and development of animal and plant systems, should be the primary objectives of future space and gravitational biology research programs. Plants exposed to artificial stressors in microgravity will have their dormant genes activated, their global systemic organization altered, and their ability to recover from future stresses, such as quickly adapting to a pathogen, improved. Strains modified for the space environment can be a useful ally for traditional engineering tactics. Our understanding of the physiology and metabolism of organisms can be improved by characterizing evolved strains and identifying the significant mutations or molecular underpinnings that enabled evolved phenotype or behavior. We can also learn the significance of molecular mechanisms contributing to strain fitness and performance. To interpret the reasoning behind the evolution-based strain improvement approach, cutting-edge metabolic identification, and characterization techniques, as well as emerging genome and transcriptome sequencing and analysis tools, are needed. These studies may provide new insights into how to increase a strain's biotic or abiotic factor tolerance, increase the use of a target substrate for growth and yield, or enhance the production of a target compound.

# “Space Biology Superhero” by combining features from these organism

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