



e-ISSN: 2319-8753 | p-ISSN: 2347-6710

# IJRSET

International Journal of Innovative Research in  
**SCIENCE | ENGINEERING | TECHNOLOGY**

# INTERNATIONAL JOURNAL OF INNOVATIVE RESEARCH

IN SCIENCE | ENGINEERING | TECHNOLOGY

Volume 11, Issue 9, September 2022

**ISSN** INTERNATIONAL  
STANDARD  
SERIAL  
NUMBER  
INDIA

Impact Factor: 8.118

 9940 572 462

 6381 907 438

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 [www.ijirset.com](http://www.ijirset.com)



# Opportunities and Challenges for Neuroscience and Neuro-Oncology in Space Travel and the Central Nervous System

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**ABSTRACT:** Pilots, astronauts, and space scientists face several obstacles in the space environment since they are continually exposed to unusual circumstances including microgravity, radiation, hypoxia, the lack of the day and night cycle, etc. Numerous physiological systems in humans are susceptible to being impacted by these stressful stimuli, which might lead to the biological and physical adaptations necessary to restore the homeostatic equilibrium. Concerns about the risks of the central nervous system (CNS) effects of spaceflight are particularly noteworthy, as multiple lines of research have shown that long-duration missions, in particular, can have a significant impact on neuroplasticity, cognitive functions, neurovestibular system, short-term memory, cephalic fluid shift, reduction in motor function, and psychological disturbances. In parallel to these possible negative impacts, there may be advantages to applying space-related circumstances to Earth-based life sciences, such as cancer research. Here, we examined the impact of actual and simulated microgravity on CNS functioning in people and cellular models, while also exploring several methods for simulating or experiencing microgravity on Earth. An emerging new area of space-based research shows that cancer cells, and brain cancer cells in particular, are severely impacted by microgravity in terms of changes to cell shape, proliferation, invasion, migration, and death. Overall, more in-depth knowledge of the ways that the space environment affects the CNS and tumour biology may be translated into a variety of clinical specialties, including oncology, neuroscience, and aerospace medicine, with the potential to provide a vast body of knowledge for the implementation of therapeutic and preventative measures.

**KEYWORDS:** Aerospace Medicine, Brain Tumors, Central Nervous System, Microgravity, Neuroscience.

## I. INTRODUCTION

Humanity has always attempted to expand its horizons throughout its evolution out of a need for information, new tools, and skills. Science and technology have made huge strides thanks to this ongoing study, and are now at the pinnacle of their development. Due to the advancement of space travel, humanity has been able to explore the cosmos beyond our planet, finding new planets and galaxies while also promoting the idea of space tourism. The short- and long-term effects of the space environment on human health are among the most pertinent issues with relation to space travel. The consequences of space missions and voyages on astronauts' health remain a major worry despite the development of technology and the efforts of highly skilled engineers to maintain the safety and performance of astronauts. Aerospace pilots are



an example of a population that frequently works in harsh environments and is regularly subjected to stressful stimuli that cause physical and biological changes that restore the homeostatic state. The term "exposome" refers to the set of environmental factors to which space and air passengers are exposed. When paired with individual features, this "space exposome" can profile the effects of space travel on the human system by reflecting the interplay of all environmental factors on the human body (Crucian et al., 2018). In order to evaluate and track the clinical, biochemical, genetic, and psychological consequences of spaceflight on human health, aerospace medicine was developed. Relevantly, the cutting-edge areas of aerospace medicine are shifting toward the newly emerging field of personalised medicine, which is based on a person's unique traits such as genes, proteins, and metabolites related to nutrition, diet, lifestyle, and environment, with the aim of integrating knowledge from various sources. It has been shown that the environment in space has an impact on practically all physiologic systems in humans. The main health risks associated with space travel include increased exposure to harmful radiation, altered gravity fields, hypoxia, the absence of the day and night cycle, vibration, acceleration, extended isolation, and confinement, as well as stress from living in a cramped and potentially unhealthy environment. Each of these concerns has a unique set of physiological and performance problems, including changes to the cardiovascular system, fluid redistribution, metabolism, and immune system; musculoskeletal issues; and motion sickness. The relevance of estimating the magnitude of space influence on human tissues and cellular models was hindered by this extensively publicised findings. As an illustration, a number of epidemiological studies looking at radiation-exposed persons found a link between radiation exposure and the development of cancer and other non-cancer health issues (Boice et al., 2018; Kamiya et al., 2015; Ozasa et al., 2019). For exploratory missions, the danger of radiation-induced carcinogenesis is regarded as a "red" risk due to its great potential for negatively affecting post-flight health and quality of life (Patel et al., 2020). Similar to this, it has been well documented that prolonged exposure to microgravity in humans results in a number of physiological and biochemical changes, including antigravity muscle atrophy, fluid shifts, and decreased plasma volume; a negative calcium balance that results in bone loss; and cardiovascular deconditioning that results in orthostatic intolerance (Wolfe & Rummel, 1992). Nevertheless, a number of studies noted that both actual and simulated microgravity had an impact on cell migration, proliferation, and death in differentiated and stem cells (Grimm et al., 2020). The potential of microgravity as a therapeutic strategy is suggested by the tight involvement of these systems in a variety of pathogenic illnesses, including as neurodegenerative diseases, ischemia, autoimmune disorders, and tumour development and progression (Prasad et al., 2020). Concerning the impacts of microgravity on the central nervous system, brain tumours require special consideration. Previous studies have shown that microgravity can slow the growth of malignant gliomas and make them more responsive to chemotherapy, suggesting that microgravity's positive effects should also be taken into account. Gliomas are the most prevalent and aggressive brain tumours, and because they have a high death rate and an average survival time of fewer than 15 months, they provide a significant treatment challenge. Notably, ground-based analogues have been created to work around some of the logistical, financial, and practical issues that prevent space investigations from progressing. Here, we give a summary of what is currently known about the impact of microgravity on the central nervous system (CNS), both in human and cellular models, based on actual spaceflight and parabolic flight investigations as well as ground-based methods appropriate for microgravity-based research. In addition, we investigate the impact of microgravity on the biology of tumour cells in this review, concentrating on brain tumour cells, in order to provide a fresh perspective on the research of cancer and somewhat novel treatment approaches.

## II. REALITY OF SPACE ENVIRONMENT

The environment in space is quite harsh for humans. Astronauts encounter stressful stimuli such radiation, microgravity, hypobaric environments, and acceleration forces, particularly during long-term missions. These stimuli then result in pathophysiological adaptive changes that are similar to many illnesses and the ageing process. Extreme space circumstances that cause human body reactions might increase our understanding of the boundaries of human beings and potentially provide prognostic signs of illnesses



(Demontis et al., 2017). The therapeutic use of radiation exposure as radiotherapy to treat primary and secondary brain cancers demonstrated the existence of radiation-induced effects on cognition, memory, learning, attention, and executive functions, as well as behavioural changes, depression, and anxiety. According to experimental studies, neuroinflammation, microvascular disruption, and a decrease in the structural complexity of neurons are all associated with radiation-induced deficits. Similar to this, CNS injury is a possibility for astronauts exposed to modest doses of protons. It has been reported that mice exposed to 0.1 to 1 Gy of whole-body proton irradiation displayed a dose-dependent loss in dendritic complexity and a substantial drop in dendritic spine quantity and density along hippocampus neurons (Parihar et al., 2015). Similar to this, recent research on mice exposed to cosmic rays found behavioural changes linked to synaptic integrity and neural structure. According to this idea, radiation reduced the spine density and dendritic complexity as well as changed the architecture of the cortical neurons that regulate neurotransmission. This in turn was accompanied by abnormalities in executive functioning, decreased fear and increased anxiety, as well as impairments in spatial and recognition memory (Parihar et al., 2016). In a retrospective research, the structural changes in the human brain during spaceflight were assessed using neuroradiological imaging and balancing data from 27 astronauts. The frontal and temporal lobe regions, in particular, showed a volumetric loss in grey matter. In the medial primary somatosensory and motor cortex, there were increases in focal grey matter. It should be noted that this result was better for ISS crew members than for shuttle crew members, indicating a space duration impact and a cumulative effect (Koppelmans et al., 2016). Due to the retroactive and heterogeneous character of the data, these findings may be viewed as speculative; hence, prospective investigations will be crucial to clarify structural brain alterations following human spaceflight. It's intriguing to hear that radiation may affect learning and memory at the cellular level through altering neuroepigenetic alterations that result in changed gene expression. Indeed, in the hippocampus of mice exposed to cosmic radiation, higher levels of the DNA-methylating enzymes DNMT3a, TET1, and TET3 were found to be associated with an increase in 5-methylcytosine (5mC) and 5-hydroxymethylcytosine (5hmC). It was discovered that this modification was connected to enduring memory deficits in the cortical and hippocampus regions. Intriguingly, the negative effects of irradiation were reversed by blocking DNA methylation, restoring mice's cognitive and behavioural abilities. The activation of rat microglia and the elevated levels of the postsynaptic density protein (PSD-95) following cosmic radiation exposure provide additional support. While changes to PSD-95 can impact synaptic integrity by upsetting the distribution and composition of proteins and receptors in the synaptic cleft, activated microglia can control structural plasticity by shortening dendritic spines and arbours (Keith & El-Husseini, 2008; Preissmann et al., 2012; Wake et al., 2013). Gravity, or G-force, governs almost all physical, chemical, and biological events on Earth, including those relating to microgravity. Gravity affects everything on Earth, and a person's weight is a measure of the gravitational pull that the Earth's gravitational field has on their mass. When an object is in orbit, it is in a state of "free fall," which can totally cancel out the effects of gravity on the item. This condition is caused by microgravity, also known as weightlessness, which is a condition in which there is less gravity than there is on the surface of the Earth. The physical and biological adaptations that take place during space missions underscore the role that gravity played in the development of humans as well as the link between microgravity, ageing, and disease onset. This loss of mechanical stimulation of cells and tissues due to the absence of normal gravity in space is the cause of many physiological issues that astronauts encounter, such as bone loss (Nabavi et al., 2011; Smith & Heer, 2002), muscle loss (Bajotto & Shimomura, 2006; Fitts et al., 2010), loss of cardiovascular capacity (Convertino, 2005; Cooke & Convertino 2005), potential wound defects (Martinez e (Crucian et al., 2011; Stowe et al., 2011). The brain is thought to be affected by microgravity at the CNS level by a variety of processes, including altered neuroplasticity, vestibular deprivation, weightlessness, and cephalic fluid shift (De la Torre, 2014). Additionally, it has been demonstrated that microgravity can change vital cell characteristics such as cell shape, proliferation, and migration (Bradbury et al., 2020; Crawford-Young, 2006). Space science continues to be very interested in gravitational biology and how it affects things like cancer cell biology and brain plasticity. As a result, we will now concentrate on the effects of microgravity on the central nervous system



(CNS), both in benign and malignant cells, and discuss the best methodologies for microgravity-based research.

## SPACEFLIGHT ANALOGUES TO INVESTIGATE MICROGRAVITY

To understand how gravity affects biological processes and organisms, microgravity research is essential. Investigations into microgravity can be conducted in special circumstances during spaceflights to the International Space Station (ISS). Since tests must be carried out autonomously, the design is reasonably challenging, the cost is greatest compared to other flight alternatives, and the preparation takes years, research in the near-Earth orbit is severely confined (Prasad et al., 2020). By dropping an airtight capsule into an evacuated tube inside a tower, such as the drop tower in Bremen, Germany (Eigenbrod, 2011), experiments in high-quality weightlessness with residual gravitational accelerations in the microgravity regime may be conducted for brief periods in true microgravity. At the Drop Tower Bremen, each freely falling experiment's maximum duration of 4.74 seconds is only constrained by the vacuum tube's height, which is entirely made of steel and encased in an outer shell of concrete. Each microgravity drop experiment in this scenario had a pure free fall height of around 110 m. (Eigenbrod, 2011). Interestingly, the capsule may also be launched from the tube's bottom up, where it will fall back, thus doubling the amount of time spent in zero-gravity. However, this will subject the experiment to another high-acceleration event (Von Kampen et al., 2006). To expose the body to microgravity for longer, parabolic flights are employed. The angle of ascent for the aircraft gets steeper until it reaches 50°, at which point the propulsion is lowered to just account for drag. After reaching its height, the aircraft descends in a nosedive that lasts for around 42 degrees before being brought back up to a horizontal flight path. In this manner, the microgravity lasts for approximately 22 seconds and is followed by two hypergravity phases that last for approximately 2 G for 20 seconds each. Following this, the aircraft climbs at an increasingly steeper angle until 50°, at which point the propulsion is reduced to solely compensate for drag (Acharya et al., 2019). Additionally, even prolonged exposure to microgravity may be achieved by taking a sounding rocket on a suborbital journey into space, which provides 6 or 13 minutes of microgravity (TEXUS/MAXUS/MAPHEUS) (Sabbatini, 2014). The "Head-down bed rest" (HDBR) method, in which the patient lays on a bed with the head inclined down by 6°, is one of the ground-based procedures used on Earth to study the effects of microgravity on human body (Messerotti Benvenuti et al., 2011). This condition may be used for both short-term (e.g., 72 hours) and long-term (e.g., 90 days) experiments, simulating many of the consequences of spaceflight on the human body, including a loss of bone density, muscle mass, and strength, and cephalic fluid shift. The 3D-clinostat, also known as the random placement machine, is the most effective tool now available to evaluate simulated microgravity on cellular models in vitro (RPM). The 3D-clinostat is a multidirectional G-force generator that has a central platform on which a cell culture flask with a cell monolayer is attached and two perpendicular arms that spin independently of one another to provide continuous rotation along two axes (Becker & Souza, 2013). In this manner, the 3D-clinostat annuls the gravity vectors at the device's core, allowing each cell to experience an average of 103 G of microgravity over time. As a result, it is feasible to see that there is no sedimentation and that 3D multicellular spheroids are growing. Since the gravity vector is continuously randomised by the RPM's continual rotation, this gadget is a helpful adjunct for setting up spaceflight investigations. The NASA-developed rotating wall vessel (RWV) bioreactor (Goodwin et al., 1993; Schwarz et al., 1992) is a specialised type of clinostat that has a horizontally rotating vessel without an internal mechanical agitator and a low shear and turbulence environment. The important findings from these studies are mentioned below. The RPM has been extensively utilised to create culture models of malignant glioma (Takeda et al., 2009), thyroid cancer (Grosse et al., 2012), and leukemic cells.

## MICROGRAVITY ON CNS

The "NASA Twins Study," a comprehensive account of the consequences of a 340-day trip on board the International Space Station, is one of the most fascinating and scientifically sound experiments studying how

the atmosphere in space affects human physiology. This comprehensive investigation detailed the consequences of a one-year mission aboard the International Space Station (ISS) on two identical twin astronauts. Longitudinal studies found spaceflight-specific alterations in the ocular structure, cognitive decline after spaceflight, gastrointestinal microbiota alterations, carotid artery distension, decreased body mass, genome instability, telomere lengthening, transcriptional and meta-bolic alterations, and DNA methylation alterations in immune and oxidative stress-related pathways. The strain of returning to Earth also had an impact on some of these changes. It's interesting to note that several alterations persisted even after six months on Earth, including decreased cognition, increased DNA damage, increased short telomere numbers, and altered gene expression levels. This behavioural, physiological, molecular, and multiomic study offers a useful overview of the known health concerns associated with human spaceflight and suggests that future long-duration space missions should be planned more effectively with specialised countermeasures (Garrett-Bakelman et al., 2019). At the CNS level, microgravity appears to cause changes to several structures and processes. For instance, when the otoliths that detect linear acceleration are abruptly devoid of the feeling of gravity, the neurovestibular system is significantly damaged. The vestibular nuclei and cortical projection, which integrate many sensory inputs, are impacted by this occurrence (Morita et al., 2016). Four cosmonauts with prior space flight experience were studied in current spaceflight research utilising electroencephalography (EEG) to track electrocortical activity. These investigations revealed an increase in the alpha rhythm in the parieto-occipital and sensorimotor areas, likely linked to gravity loss (Cheron et al., 2006). More recently, it has been observed that microgravity reduced the alpha rhythm of the cerebellum, the vestibular system, and the bilateral motor cortex in astronauts who were free-floating onboard the International Space Station before and after the space journey (Cebolla et al., 2016). These findings draw attention to the greater need for vestibular integration of incongruent information as well as the additional processing required for postural stabilisation (Cebolla et al., 2016). A dry immersion investigation, while also supported the decline in alpha power, also revealed a little rise in theta power (Kuznetsova et al., 2015). Parallel to this, investigations on parabolic flight revealed a decline in beta power, which could be an emotional response to the lack of gravity, baroreceptor stimulation, or reduced excitation levels (Lipnicki, 2009; Schneider et al., 2008). Relevantly, HBDR investigations found contradictory outcomes, including increased alpha, beta, and theta power. These findings may be explained by the fact that HBDR retains the gravitational input, making it a poor model for studying how the human brain responds to microgravity. Additionally, dry immersion and HBDR are linked to a sensation of immobility and monotony if changes in electrocortical activity during parabolic and space-flight indicate elevated emotional stress levels (Marui et al., 2014). Additionally, in vivo structural, metabolic, functional, and vascular alterations brought on by microgravity were successfully detected using magnetic resonance imaging (MRI). According to a new case study, long-term spaceflight causes considerable changes in human brain functioning, as well as abnormalities in the functional connection between the cerebellum and motor cortex and changes to the supplementary motor region (Demertzi et al., 2016). Another observation relates to the rise in intracranial pressure (ICP), which is determined by combining variations in the volumetric characteristics of the brain, the morphology of the pituitary, and the hydrodynamics of the aqueduct carrying cerebrospinal fluid (CSF). Long-duration spaceflight was associated with enhanced pituitary deformation, amplified CSF hydrodynamics, and expansion of the combined brain and CSF volumes, according to a comparison of these parameters before and after the trip. According to a recent study, combined brain and CSF volume increase continued for up to a year after recovery, indicating possible long-term changes (Kramer et al., 2020). Interestingly, in this context, NASA in 2010 referred to this rise in ICP as Visual Impairment Intracranial Pressure Syndrome, but in 2017 it was modified to Spaceflight Associated Neuro-Ocular Syndrome (SANS), as raised ICP was not seen to be the main problem (Lee et al., 2017). In contrast, Lawley et al. observed that extended durations of simulated microgravity did not result in successive rises in ICP, furthering the notion that the daily circadian cycles, without which disease may emerge, may preserve the human brain (Lawley et al., 2017). Neuroplasticity needs special consideration in the study of the effects of microgravity on the central nervous system. The concept of neuroplasticity refers to the brain's capacity to rearrange its structure and associated processes in response to demanding stimuli or environmental factors. Numerous techniques



are used to research neuroplasticity, including MRI, EEG with evoked potentials (ERPs), transcranial magnetic stimulation (TMS), changes in activity patterns, map size and excitability, and task- or resting-state brain activity (Van Ombergen et al., 2017). According to HDBR ground investigations, micro-gravity reduces brain activity by amplifying the delta and theta EEG low-frequency oscillations (Vaitl et al., 1996). Notably, learning is a crucial cognitive function in extended space missions, and cortical plasticity is directly tied to learning. For instance, a startle reflex habituation research has been carried out to assess learning and brain plasticity damage in HDBR participants compared to seated controls (Messerotti Benvenuti et al., 2011). The study showed a microgravity-induced lack of startle reflex plasticity in HDBR subjects, which is consistent with earlier research reporting an impairment in astronauts' sensory, motor, and complex cognitive activity (Manzey & Lorenz, 1998) and suggests that further understanding of learning and reasoning in the space environment is essential for the success of future long-term space missions (Messerotti Benvenuti et al., 2011). According to other research, the extended HDBR approach had a negative impact on each person's executive functioning, mood, and physiological activity (Liu et al., 2012), as well as on postural stability and reduced functional mobility (Muir et al., 2011). (Reschke et al., 2009). In parallel, Liao et al. reported a decrease in grey matter in frontal brain regions and small grey matter increases in posterior parietal regions in 18 subjects. Roberts et al. observed brain tissue expansion in the central frontoparietal regions and contraction in orbitofrontal regions in subjects in HDBR state (Liao et al., 2012; Roberts et al., 2010). They observed that HDBR reduced cortical activity in the motor regions associated with leg representation, and that TMS also reduced corticospinal excitability. They made the interesting observation that the functional mobility impairment decreased in proportion to the increase in motor cortical activity. A few years later, Liao et al. found that after 72 hours of HDBR, there was also less connection in the thalamus during rest (Liao et al., 2012). More recently, Pechenkova et al. used functional MRI to examine changes in functional brain connectivity in astronauts following a prolonged space mission. According to the scientists, a plantar stimulation activity caused distinct modifications in functional brain connections. Increased connection between the right and left insulae, as well as between the right posterior supramarginal gyrus and the remainder of the brain, was the outcome of the changes seen. The right inferior parietal cortex, vestibular nuclei, and cerebellum, on the other hand, were shown to have diminished connection with regions related to motor, visual, vestibular, and proprioception activities. Although the effects of the readjustment to earth gravity that took place between the time of landing and the post-flight fMRI cannot be solely attributed to exposure to microgravity, the effects may still be very significant for future research into neural plasticity adaptation related to microgravity (Pechenkova et al., 2019). According to the data, space passengers experience a number of difficulties, including radiation and microgravity, which might combine to affect cognition, learning, and memory.

### III. CELLULAR STUDIES AND IN VIVO NON-CANCER CELLS

The effects of microgravity on the nerve cells in the human brain are the subject of an intriguing area of research. The cytoskeletal structure and cellular organelles' spatial relationship is adjusted by G-force, which has an impact on the metabolic processes. As a result, gravity has an effect on cytoarchitectural biology at the cellular level, affecting protein coding, transport, metabolism, DNA replication, and RNA transcription. Oligodendrocytes are the glial cells that create and maintain myelin in the central nervous system (CNS). The development of tightly wound myelin segments by oligodendrocytes, which enable the saltatory conduction of electric impulses, ensures the neural transmission. According to studies, oligodendrocytes exposed to simulated microgravity exhibited enhanced glycolysis and mitochondrial respiration as well as fatty acid production and secretion (Espinosa- Jeffrey et al., 2016). Mesenchymal stem cells been shown to differentiate more readily into neurons under microgravity, indicating a new treatment approach for CNS degenerative illnesses. In fact, rat mesenchymal stem cells cultivated in normal gravity displayed lower levels of microtubule-associated protein-2 (MAP-2), tyrosine hydroxylase (TH), and choline acetyltransferase (CHAT) than those cultured in a neuronal differentiating media and in a clinostat imitating microgravity. Additionally, these cells generate more neurotrophins including nerve growth factor (NGF)



and brain-derived growth factor (BDNF) (Chen et al., 2011). It's interesting to note that gravity has an impact on the behaviour of bone marrow stromal cells (BMSCs), which have gained attention for the treatment of CNS illnesses. For instance, a research on BMSCs taken from mice and cultivated in a medium for neural differentiation found that, in contrast to BMSCs cultured in microgravity, neural-induced BMSCs cultured at 1 G showed neural development. Additionally, BMSCs cultivated in simulated microgravity demonstrated better survival in the wounded area after intravenous injection in a mouse model of cerebral contusion, expressing elevated levels of CXCR4 on cell membrane. Additionally, the transplanted mice's motor function greatly improved (Yuge et al., 2011). Oxidative stress is a possible issue with microgravity exposure. For instance, oxidative mechanisms in the hippocampus are strongly linked to the increased activation of glucocorticoid receptors during stress response, such as microgravity. A fascinating experiment was carried out by Sarkar et al. on mice suspended by their tails in the middle of the cage, yet allowed to touch the floor with their front paws, and left for 7 days. The data showed that pyruvate dehydrogenase (PDK-1) and  $\alpha$ -synuclein levels in mice hippocampi decreased (Sarkar et al., 2008). A molecular chaperone called  $\alpha$ -synuclein is well recognised for preventing the aggregation of non-conforming proteins. The prevalence of abnormal protein aggregations may rise as a result of the lower amount of  $\alpha$ -synuclein seen in the microgravity condition. On the other side, PDK-1 inhibits apoptosis, which influences cellular responses to hypoxia and oxidative stress. It also regulates glucose and fatty acid metabolism and homeostasis. A recent study used the hindlimb unloading (HLU) technique and/or low-dose  $\gamma$ -ray irradiation to simulate microgravity in order to evaluate the long-term transcriptional consequences of spaceflight analogue circumstances in a mouse model (LDR). The findings showed that following a single HLU or LDR treatment, there was barely any change in gene expression and cytosine methylation. The opposite was true, however, as a combination of HLU and LDR resulted in several changes in gene expression and promoter methylation in pathways implicated in neurogenesis, neuroplasticity, and the regulation of neuropeptides, as well as dysregulated cell shape and signalling (Overbey et al., 2019). Characterizing the proteome alterations in mouse brain after a 13-day trip aboard the Space Shuttle Atlantis is a fascinating research on mice (STS-135). 26 proteins were found to have changed in grey and white matter following spaceflight, according to the quantitative proteomic study. These proteins were discovered to be connected to protein transport, metabolism, vesicular activity, synaptic plasticity, and neuronal structure, indicating the major influence of space missions on the integrity and structure of the brain (Mao et al., 2018). For the protection of the human body during space missions, the space environment poses a significant obstacle. Although microgravity may have negative effects on human physiology and the central nervous system, there are also a sizable number of possible health advantages associated with space settings. The support structures consisting of proteins and carbohydrates in the human body allow cells to develop regularly while maintaining their three-dimensional forms. On Earth, cells develop into monolayers that are flat or into floating forms that are exposed to normal gravity. Cells organise into three-dimensional aggregates in space, which have less fluid shear stress. Joshua Chou, a researcher in biomedical engineering at the University of Technology Sydney, began studying the behaviour of cancer cells in zero gravity in 2014, building on his earlier work on how to avoid bone loss in space (Bradbury et al., 2020). The understanding of tumour development mechanisms and any possible treatment responses may both benefit from research on cancer growth in variable gravity conditions. Due to the effects of microgravity on cell shape, proliferation, invasion, migration, apoptosis, and gene expression, increased focus has been paid to the effects of microgravity on cellular activities, particularly on tumour cells. Colon cancer cells were subjected to simulated microgravity in a study, and the results showed 1801 upregulated genes involved in transcriptional regulation, proteolysis, negative regulation of cell growth, and programmed cell death, and 2542 downregulated genes involved in DNA repair, DNA replication, and cell cycle (Vidyasekar et al., 2015). According to studies by Grimm et al. (2014) and Ulbrich et al. (2014), both real and simulated microgravity was able to stimulate 3D development in many cells by reorganising the cytoskeleton and counteracting sedimentation. Simulated weightlessness caused human breast cancer cells to lose their cyokeratin network and chromatin structure as well as change their microtubule structure. Additionally, mitosis was extended and the cell cycle was halted, which resulted in a decrease in cell proliferation. Similar to this, human MCF-7 cells subjected to microgravity mimicked





by clinorotation experienced disorganisation of microfilaments and microtubules. These microfilaments did not exhibit the normal radial array, which disrupted the microtubules. Additionally, focal adhesions had decreased quantity and clustering compared to those formed in controls, and they were less developed (Li et al., 2009). Clinostat's simulation of microgravity has also been shown to reduce the growth, migration, and invasion of A549 human lung adenocarcinoma cells, indicating a significant potential for reducing cancer spread (Chang et al., 2013). Additionally, when cultivated in clinostat-simulated microgravity, human follicular thyroid cancer cell line ML-1 had elevated levels of the apoptosis-associated Fas protein and Bax as well as a reduction in the antiapoptotic Bcl-2 (Kossmehl et al., 2003). Likewise, when exposed to simulated microgravity, thyroid carcinoma cells ONCO-DG1, gastric carcinoma cells SGC-7901, MDA-MB-231 breast cancer cells, and BL6-10 melanoma cells displayed enhanced apoptosis (Grimm et al., 2002; Kossmehl et al., 2003; Masiello et al., 2014; Zhu et al., 2014).

These findings demonstrate that, in contrast to normal gravity, tumour cells undergo changes that include cell aggregation, cytoskeleton rearrangement, cell cycle arrest, migration, and death. For the protection of the human body during space missions, the space environment poses a significant obstacle. Although microgravity may have negative effects on human physiology and the central nervous system, there are also a sizable number of possible health advantages associated with space settings. The support structures consisting of proteins and carbohydrates in the human body allow cells to develop regularly while maintaining their three-dimensional forms. On Earth, cells develop into monolayers that are flat or into floating forms that are exposed to normal gravity. Cells organise into three-dimensional aggregates in space, which have less fluid shear stress. colon cancer cells exposed to simulated microgravity had their expression profiled, and the results showed 1801 upregulated genes involved in transcriptional regulation, proteolysis, negative regulation of cell growth, and programmed cell death, and 2542 downregulated genes involved in DNA repair, DNA replication, and cell cycle (Vidyasekar et al., 2015). According to studies by Grimm et al. (2014) and Ulbrich et al. (2014), both real and simulated microgravity was able to stimulate 3D development in many cells by reorganising the cytoskeleton and counteracting sedimentation. Simulated weightlessness caused human breast cancer cells to lose their cyokeratin network and chromatin structure as well as change their microtubule structure. Additionally, mitosis was extended and the cell cycle was halted, which resulted in a decrease in cell proliferation (Vassy et al., 2003). Similar to this, human MCF-7 cells subjected to microgravity mimicked by clinorotation experienced disorganisation of microfilaments and microtubules. These microfilaments did not exhibit the normal radial array, which disrupted the microtubules. Additionally, focal adhesions had decreased quantity and clustering compared to those formed in controls, and they were less developed (Li et al., 2009). Clinostat's simulation of microgravity has also been shown to reduce the growth, migration, and invasion of A549 human lung adenocarcinoma cells, indicating a significant potential for reducing cancer spread (Chang et al., 2013). Additionally, when cultivated in clinostat-simulated microgravity, human follicular thyroid cancer cell line ML-1 had elevated levels of the apoptosis-associated Fas protein and Bax as well as a reduction in the antiapoptotic Bcl-2 (Kossmehl et al., 2003). Likewise, when exposed to simulated microgravity, thyroid carcinoma cells ONCO-DG1, gastric carcinoma cells SGC-7901, MDA-MB-231 breast cancer cells, and BL6-10 melanoma cells displayed enhanced apoptosis (Grimm et al., 2002; Kossmehl et al., 2003; Masiello et al., 2014; Zhu et al., 2014). These findings demonstrate that, in contrast to normal gravity, tumour cells undergo changes that include cell aggregation, cytoskeleton rearrangement, cell cycle arrest, migration, and death.

CNS tumours afflict over 200,000 individuals annually and account for about 2% of all cancer-related deaths, making them a significant cause of morbidity and mortality globally (GBD 2019). The World Health Organization (WHO) has established a grading system for CNS tumours, with grades I and IV, often known as high-grade gliomas, ranging from the least aggressive with the best prognosis to the most malignant with the worst prognosis (HGGs). Glioblastoma (GBM) is the most prevalent and malignant HGG, and it poses the greatest treatment challenge with a dismal prognosis of just 14 months and a 5% 5-year survival rate (Wipfler et al., 2018). Intense angiogenesis, invasion, cell infiltration, fast progression, resistance to radio-



and chemotherapies, and a high rate of relapse are characteristics of GBM. The current accepted standard of care for the treatment of GBM is for gross complete resection whenever feasible, followed by radiotherapy, chemotherapy, and adjuvant temozolomide (TMZ) (Weller et al., 2017). Only marginal prognostic gains have been made in spite of this intensive treatment regimen and the development of novel strategies including molecular target therapy and immunotherapy. Notably, a subset of tumorigenic stem-like cells known as GBM stem cells (GSCs) that may hierarchically begin, sustain, and propagate the neoplasm is primarily responsible for GBM resistance to therapy and the high frequency of recurrence. GSCs are genetically unstable, self-renewing, pluripotent, and very proliferative (Pesenti et al., 2019). These factors need the creation of innovative therapeutic strategies, and recent research demonstrating the weightlessness of glioma cells has shown considerable promise for prospective clinical applications.

In several research, 3D-clinostat has been used to assess how glioma cells respond to simulated microgravity. An Italian research on C6-glioma cells that were placed on a 3D-clinostat for 15, 30, 1, 20, and 32 hours found that the cortical layer was disrupted, filopodia decreased, microtubules appeared extremely disordered, and radial disposition was lost after 30 minutes of simulating microgravity. Additionally, blebs that protruded from the nuclear membrane, chromatin condensation within the nuclei, and DNA breakage were seen along with the altered nuclear shape (Uva et al., 2002). Human malignant glioma cell lines D54MG, U251MG, and T98G were cultivated in a different research using 3D-clinostat to investigate growth and chemosensitivity in comparison to normal gravity conditions. The findings showed that, without affecting cell viability, microgravity drastically reduces mitochondrial activity and cell growth rate. As a result, the slowing of mitosis may be the cause of proliferation inhibition. Interestingly, cells grown in clinostat demonstrated increased chemo-sensitivity to the anticancer drug cisplatin, pointing to a possible therapeutic benefit of microgravity (Takeda et al., 2009). More recently, the impact of simulated microgravity on the capacity of human glioblastoma U87 cells to invade and migrate has been studied. According to the study, microgravity can reduce invasion and migratory potentials by decreasing store-operated calcium entry and downregulating the expression of Orai 1, a crucial calcium channel (SOCE). Because Orai1 is a novel molecular regulator of tumorigenicity and stemness, it may be possible to treat cancer by blocking Orai1 signalling, and the use of microgravity may be an effective treatment option for GBM (Shi et al., 2015). Another piece of evidence is the finding that simulated microgravity suppresses the proliferation of U251 malignant glioma cells and causes them to undergo apoptosis by upregulating the expression of p21 and downregulating the expression of insulin-like growth factor binding protein-2 (IGFBP-2). Notably, IGFBP-2 has exhibited on-cogenic effects include boosting proliferation, driving invasion, and inhibiting apoptosis, whereas p21 is known to inhibit tumour development by causing cell cycle arrest (Zhao et al., 2017). Moreover, GBM from surgical patients has been utilised to explore the architectural changes caused by the effects of simulated microgravity at the macroscopic level. To achieve this, GBM cells were cultivated using the tissue block culture method before being put through various timings of static culture or rotating treatment. At the conclusion of the experiment, it was shown that extended rotation led to an expansion of cell somas and a decline in cell adhesion. High levels of cytoskeleton instability were discovered using immunofluorescent labelling, which resulted to microgravity-induced apoptosis and migration inhibition (Wang et al., 2016). An innovative hybrid in vitro vascularized GBM-on-a-chip model has recently been developed by the Joshua Chou group by cleverly combining microfluidics and 3D bioprinting technologies. This model replicates the brain tumour microenvironment, including the functional blood-brain barrier (BBB) and the perivascular niche. This model, which serves as an unique and practical tool for preclinical research in neuro-oncology, was utilised to assess the influence of microgravity conditions in terms of mechanobiology. The absence of gravity prevents GBM cell invasion and aggregation without impairing cell survival, as can be seen by the RPM. This serves as more confirmation that GBM spheroid formation, typical of GSC development, is gravity dependent, compromising GBM fundamental cell activities and processes in microgravity (Silvani et al., 2021). The GlioSat/GlioLab project began in 2009 with the goal of examining the combined impact of microgravity and ionising radiation on the prognosis of GBM cancer cells. A cell set was observed in parallel in orbit and on



the ground as part of this project, sponsored by the Group of Astrodynamics of University of Roma La Sapienza at the School of Aerospace Engineering in Roma, the Space Science Center at Morehead State University in Kentucky, and the Genetic Department of IRCCS-Hospital CSS San Giovanni Rotondo in Italy, to compare the behaviour of tumour cells. Two preliminary Space Shuttle missions have already been completed, STS-134 and STS-135, and the findings of the DNA analysis confirm the original intent of the GLioLab/Gliosat project, justifying the further study (Cappelletti et al., 2012).

With the help of an inventive series of research projects, the ISS's distinctive microgravity environment is enabling further improvements in cancer therapy. In particular, a technique called microencapsulation may create small, liquid-filled, biodegradable micro-balloons that can be administered precisely to specific locations within a cancer patient. This effectively revolutionises cancer therapy. Dr. Dennis Morrison of NASA's Johnson Space Center has been using the space station's microencapsulation experiments to advance the development of the Microencapsulation Electrostatic Processing System-II (MEPS-II). MEPS-II microcapsules containing anticancer medications have been administered into human lung and prostate cancers in animal models in laboratory studies, indicating enhanced site-specific therapeutic effects and the prevention of tumour development (<https://www.nasa.gov>). A few years ago, the Cambridge, Massachusetts-based biotechnology company Angiex established a Model System for Evaluation of Cancer Therapy Toxicity, looking at the proliferation of endothelial cells (ECs), which make up blood vessels, in a microgravity environment. The study's main premise is that ECs grown in microgravity provide a reliable model for evaluating the effects of drugs that target the vascular system. According to NASA, the discovery may make it possible to design vascular-targeted medications that are safer and more efficient without using animal testing. Most research on in vivo cancer models has concentrated on the immune system since microgravity may alter both innate and adaptive immune systems. For instance, during the Soyuz, Skylab, Salyut, and Space Shuttle projects, it was shown that immune cell performance was closely correlated with flight periods, with a 50% drop in lymphocytic response post-mission compared to pre-flight (Konstantinova et al., 1993; Topal & Zamur, 2021). A reduction in T cell percentages, numbers, responses to a strong mitogen, and cytokine production, all of which are crucial mechanisms for an effective immune defence and homeostasis, have been described as one of the consequences of microgravity on immune cells in mice (Gridley et al., 2009; Sonnenfeld et al., 1992). According to a research by Shi et al. employing mouse hematopoietic stem and progenitor cells, microgravity significantly reduced macrophage number, differentiation, and functional polarisation, which led to alterations in gene expression patterns (Shi et al., 2021). Cancer and the immune system are closely related because immune response problems can lead to the development of cancer or make it more resistant to treatment. Numerous investigations showed a connection between microgravity and the immune system, including immune cell activation and the generation of inflammatory cytokines (Corthay, 2014; Mukhopadhyay et al., 2016). Therefore, we may say that microgravity may be a useful immunomodulation technique. When considered collectively, experimental research on exposure to the space environment actually advances our understanding of how microgravity affects the development of cancer cells and provides a fresh framework for creative approaches. We may be able to better comprehend pathologies and research and test preventative strategies for both future space missions and terrestrial illnesses by combining the resources available in the distinctive space environment with cutting-edge Earth technology.

#### IV. FUTURE ASPECTS & CONCLUSION

Exploration and discovery have an infinite horizon in space. Cells and tissues subjected to changed gravity circumstances undergo a variety of molecular, physiological, and morphological alterations. In the medical arena, particularly in neurology and cancer, the microgravity-induced changes in physiological cell biology, such as cell cycle progression, cytoskeleton remodelling, and apoptotic processes are directly transferable, expediting and advancing life science research. Understanding how microgravity affects CNS processes and the fundamental mechanisms by which these changes happen will be important for minimising the impacts

of long-term exposure of people to partial gravity and weightlessness as well as for developing countermeasures. To undertake, combine, and optimise various topic investigations and provide a detailed picture of the functional, structural, and biochemical brain changes related to spaceflight, a multidisciplinary taskforce would be extremely exciting in this regard.

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PMID: 25117363.



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