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Research Article,

Challenges and Opportunities for Neuroscience in the Context of Space Flight and the Central Nervous System

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Abstract:

Pilots, astronauts, and space scientists face numerous 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 could 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 addition to these potential negative impacts, there may be advantages to applying space-related conditions to Earth-based life sciences, such as cancer research. Here, we examined the impact of actual and simulated microgravity on CNS functions in humans 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 negatively impacted by microgravity in terms of changes to cell shape, proliferation, invasion, migration, and death.

Keywords: aerospace medicine, brain tumors, central nervous system, microgravity, neuroscience

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 research, and are now at the pinnacle of their development. Due to the advancement of space travel, humanity has been able to explore the universe 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 serious worry despite the development of technologies and the efforts of highly qualified 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 travellers are exposed. When paired with individual features, this "space exposome" can profile the effects of space travel on the human system by reflecting the interaction of all environmental factors on the human body (Crucian et al., 2018). In order to examine and

keep track of 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 moving in the direction of the newly emerging field of personalised medicine, which is based on unique traits such as a person's 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. Higher levels of harmful radiation, altered gravity fields, hypoxia, the absence of the day and night cycle, vibration, acceleration, prolonged isolation, and confinement, as well as stress resulting from a closed and potentially hostile living environment, are among the major health risks of space travel. Any of these concerns is linked to a unique set of physiological and performance risks, including changes in the immune system, metabolism, metabolism, and cardiovascular functions; muscular diseases; and motion sickness. The importance of estimating the scope 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). Comparable 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 real 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 impact 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 mortality rate and an average survival time of fewer than 15 months, they pose a significant therapeutic challenge. Notably, ground-based analogues have been created to address some of these issues because space research are constrained by a number of logistical, financial, and practical limitations. Below, 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. Additionally, 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 study of cancer and somewhat novel therapeutic approaches.

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 diseases and the ageing process. Extreme space environment-induced human body reactions may increase our understanding of the boundaries of human beings and may perhaps disclose prognostic signs of diseases (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, radiation-induced deficits

are associated with a decrease in the structural complexity of neurons, neuroinflammation, and microvascular disruption. 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 significant 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 was followed by deterioration of spatial and recognition memory, deficiencies in executive processes, decreased fear, and elevated anxiety (Parihar et al., 2016). In a retrospective study, the structural changes in the human brain following spaceflight were examined using neuroradiological pictures 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 effect 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 changes following human spaceflight. A fascinating new study suggests that radiation may cause neuroepigenetic changes at the cellular level that affect learning and memory by altering 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 function. 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 affect 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. Once an object experiences "free fall," as it does in orbit, the gravitational pull of gravity can be entirely negated. This condition is brought on 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 evolution 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 mechanisms, 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. When an object experiences "free fall," as it does

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The effects of gravity on biological processes and organisms must be revealed through microgravity research.

To investigate microgravity, spaceflights to the International Space Station (ISS) offer special circumstances. Since tests must be carried out autonomously, the design is reas- sonably 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 can 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). Notably, the capsule can 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 used. As the angle of ascent increases until it reaches 50°, the propulsion is lowered to only 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 can be achieved by taking a sounding rocket on a suborbital flight 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 subject lies 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 can 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 made up of a central platform on which a cell culture flask with a cell monolayer is attached, joined to two perpendicular arms that rotate separately from one another to provide continuous rotation along two

axes (Becker & Souza, 2013). 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 numerous structures and functions. For instance, when the otoliths that detect linear acceleration are abruptly devoid of the sense of gravity, the neurovestibular system is particularly impacted. 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 studies 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 noted 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 flight (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). Furthermore, a study using dry immersion found that theta power had somewhat increased but alpha power had decreased (Kuznetsova et al., 2015). Parallel to this, investigations on parabolic flight revealed a decline in beta power, which might 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 elevated alpha, beta, and theta power. These findings may be explained by the fact that HDBR preserves the gravitational input, making it a poor model for studying how the human brain responds to microgravity. Additionally, dry immersion and HDBR are linked to a sense of immobility and monotony if changes in electrocortical activity following 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 cerebrospinal fluid (CSF) aqueduct. Long-duration spaceflight was associated with increased pituitary deformation, amplified CSF hy- drodynamics, 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 thought to be the main problem (Lee et al., 2017). On the other hand, Lawley et al. showed that extended durations of simulated microgravity did not result in successive rises in ICP, promoting the theory that the daily circadian cycles, without which disease may emerge, may preserve the human brain. 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 organise its structure and related processes in response to demanding stimuli or environmental factors. Neuroplasticity can affect a variety of structures, from brain networks to synaptic plasticity at the cellular level. 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. According to HDBR ground investigations, micro-gravity reduces brain activity by amplifying the delta and theta EEG low-frequency rhythms (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 injury in HDBR participants compared to sitting controls. 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 additional knowledge of learning and reasoning in the space environment is essential for the success of future long-term space missions (Messerotti). In addition to its detrimental effects on postural stability (Muir et al., 2011), impaired functional mobility, and individual executive functioning, emotion, and physiological activity, prolonged HDBR method was also found to have negative effects on postural instability in other studies (Liu et al., 2012). (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 (Roberts et al., 2010). They documented a reduction in cortical activity caused by HDBR in the motor regions with leg representation as well as a reduction in corticospinal excitability using TMS. 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 authors, 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 result of the changes seen. The right inferior parietal cortex, vestibular nuclei, and cerebellum, on the other hand, were found 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 could combine to affect cognition, learning, and memory. CNS tumors represent a substantial source of morbidity and mortal- ity worldwide, affecting about 200,000 people every year and rep- resenting approximately 2% of cancer deaths (GBD 2019). The World Health Organization (WHO) specifies a grading system for CNS tu- mors ranging from grade I, the least aggressive with the best prognosis, to grade IV, the most malignant with worst prognosis, also known as high-grade gliomas (HGGs). Among HGGs, glioblastoma (GBM) is the most frequent and malignant, with a poor prognosis of about 14 months and a 5-year survival rate at 5% (Wipfler et al., 2018), representing an extreme therapeutic challenge. GBM is character- ized by intense angiogenesis, invasion, cell infiltration, rapid progres- sion,

resistance to radio- and chemotherapies, with high frequency of relapse. 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 pathways. 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 have shown to differentiate more readily into neurons in 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 differential media and in a clinostat imitating microgravity. Additionally, these cells secrete more neurotrophines, such as brain-derived growth factor (BDNF) and nerve growth factor (NGF), than other cells (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 study 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 differentiation. Additionally, BMSCs cultivated under 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 potential 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 -synuclein levels in mice hippocampi decreased (Sarkar et al., 2008). A molecular chaperone called -synuclein is well known for preventing the aggregation of non-conforming proteins. The prevalence of abnormal protein aggregations may rise as a result of the lower level of -synunclein seen in the microgravity state. By shielding cells from apoptosis, PDK-1, on the other hand, regulates fatty acid and glucose metabolism and homeostasis, affecting cellular responses to oxidative stress and hypoxia. A recent study used the hindlimb unloading (HLU) technique and/or low-dose -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. Contrarily, a combination of HLU and LDR led to many changes in gene expression and promoter methylation in pathways related to neurogenesis, neuroplasticity, and the regulation of neuropeptides, as well as dysregulated cell shape and signalling (Overbey et al., 2019). Characterizing the proteome changes in mouse brain after a 13-day trip on the Space Shuttle Atlantis is a fascinating study on mice (STS-135). 26 proteins were found to have changed in grey and white matter after spaceflight, according to the quantitative proteomic study. These proteins were discovered to be linked to protein transport, metabolism, vesicular activity, synaptic plasticity, neuronal structure, and more, indicating that space missions have had a substantial impact on the health and integrity 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 impacts on human physiology and the central nervous system (CNS), there are also a sizable number of potential 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 shapes. On Earth, cells develop in monolayers that are flat or in floating forms that are sensitive to earth's gravity. Cells organise into three-dimensional aggregates in space, which have less fluid shear stress. Following his prior work on how to avoid bone loss in space, Joshua Chou, a biomedical engineering researcher at University of Technology Sydney, began his investigations on cancer cells' behaviour at zero gravity in 2014. (Bradbury et al., 2020). The understanding of tumour development mechanisms and any potential therapeutic responses may both benefit from research on cancer growth in variable gravity conditions. Due to the fact that microgravity affects cell shape, proliferation, invasion, migration, apoptosis, and gene expression, increased focus has been paid to how it influences cellular activities, particularly in tumour cells. Table 1 contains some of the most pertinent experimental evidence, which will be briefly explored here. Colon cancer cells were subjected to simulated microgravity in a study, and the results showed 1801 upregulated genes with functions related to transcriptional regulation, proteolysis, negative regulation of cell growth, and programmed cell death, and 2542 downregulated genes with functions related to 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 cytokeratin 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 exposed to microgravity mimicked by clinorotation experienced disorganisation of microfilaments and microtubules. These microfilaments did not exhibit the typical radial array, which disrupted the microtubules. Additionally, focal adhesions had decreased number 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 decrease 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 apoptosis.

Conclusion:

Exploration and discovery have an infinite horizon in space. Cells and tissues subjected to changed gravity conditions undergo a variety of molecular, physiological, and morphological alterations. In the medical arena, particularly in neuroscience and oncology, the microgravity-induced changes in physiological cell biology, such as cell cycle progression, cytoskeleton remodelling, and apoptotic mechanisms, are directly transferable, expediting and enhancing life science research. Understanding how microgravity affects CNS processes and the fundamental mechanisms by which these effects 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. It would be extremely interesting in this situation to establish a multidisciplinary taskforce to undertake, combine, and optimise various topic investigations and produce a detailed picture of the functional, structural, and biochemical brain changes related to spaceflight.

Reference:

[1] Acharya, A., Brungs, S., Lichterfeld, Y., Hescheler, J., Hemmersbach, R., Boeuf, H., & Sachinidis, A. (2019). Parabolic, flight-induced, acute hypergravity and

microgravity effects on the beating rate of human cardiomyocytes. Cell, 8, 352.

[2] Acharya, M. M., Baddour, A. A. D., Kawashita, T., Allen, B. D., Syage, A. R., Nguyen, T. H., Yoon, N., Giedzinski, E., Yu, L., Parihar, V. K., & Baulch, J. E. (2017). Epigenetic determinants of space radiation- induced cognitive dysfunction. Scientific Reports, 7, 42885.

[3] Bajotto, G., & Shimomura, Y. (2006). Determinants of disuse-induced skeletal muscle atrophy: Exercise and nutrition countermeasures to prevent protein loss. Journal of Nutritional Science and Vitaminology (Tokyo), 52, 233–247.

[4] Becker, J. L., & Souza, G. R. (2013). Using space-based investigations to inform cancer research on earth. Nature Reviews. Cancer, 13, 315–327.

[5] Boice, J. D., Jr., Ellis, E. D., Golden, A. P., Girardi, D. J., Cohen, S. S.,

[6] Chen, H., Mumma, M. T., Shore, R. E., & Leggett, R. W. (2018). The past informs the future: An overview of the million worker study and the Mallinckrodt chemical works cohort. Health Physics, 114, 381–385.

[7] Bradbury, P., Wu, H., Choi, J. U., Rowan, A. E., Zhang, H., Poole, K., Lauko, J., & Chou, J. (2020). Modeling the impact of microgravity at the cel- lular level: Implications for human disease. Front Cell Developmental Biology, 8, 96.

[8] Cappelletti, C., Notarangelo, A., & De Moss, D. (2012). Study of glio- blastoma cancer cells behaviour inside space shuttle. In 63rd International Astronautical Congress 2012, IAC 2012 (Vol. 1, pp. 482–

[9] 488). Elsevier.

[10] Cebolla, A. M., Petieau, M., Dan, B., Balazs, L., McIntyre, J., & Chéron, G. (2016). Cerebellar contribution to visuo-attentional alpha rhythm: Insights from weightlessness. Scientific Reports, 6, 37824.

[11] Chang, D., Xu, H., Guo, Y., Jiang, X., Liu, Y., Li, K., Pan, C., Yuan, M., Wang, J., Li, T., & Liu, C. (2013). Simulated microgravity alters the meta- static potential of a human lung adenocarcinoma cell line. In Vitro Cellular & Developmental Biology, 49, 170–177.

[12] Chen, J., Liu, R., Yang, Y., Li, J., Zhang, X., Li, J., Wang, Z., & Ma, J. (2011).

[13] The simulated microgravity enhances the differentiation of mesen- chymal stem cells into neurons. Neuroscience Letters, 505, 171–175. Chen, Z. Y., Jiang, N., Guo, S., Li, B. B., Yang, J. Q., Chai, S. B., Yan, H. F.,

[14] Sun, P. M., Zhang, T., Sun, H. W., Yang, H. M., Zhou, J. L., & Cui, Y. (2020). Effect of simulated microgravity on metabolism of HGC-27 gastric cancer cells. Oncology Letters, 19, 3439–3450.

[15] Cheron, G., Leroy, A., De Saedeleer, C., Bengoetxea, A., Lipshits, M., Cebolla, A., Servais, L., Dan, B., Berthoz, A., & McIntyre, J. (2006). Effect of gravity on human spontaneous 10-Hz electroencephalo- graphic oscillations during the arrest reaction. Brain Research, 1121, 104–116.

[16] Convertino, V. A. (2005). Consequences of cardiovascular adaptation to spaceflight: Implications for the use of pharmacological counter- measures. Gravit Space Biol Bull., 18, 59–69.

[17] Cooke, W. H., & Convertino, V. A. (2005). Cardiovascular consequences of weightlessness promote advances in clinical and trauma care. Current Pharmaceutical Biotechnology, 6, 285–297.

[18] Corthay, A. (2014). Does the immune system naturally protect against

[19] cancer? Frontiers in Immunology, 5, 197.

[20] Crawford-Young, S. J. (2006). Effects of microgravity on cell cytoskele- ton and embryogenesis. The International Journal of Developmental Biology, 50, 183–191.

[21] Crucian, B., Stowe, R., Quiriarte, H., Pierson, D., & Sams, C. (2011). Monocyte phenotype and cytokine production profiles are dys- regulated by short-duration spaceflight. Aviation, Space, and Environmental Medicine, 82, 857–862.

[22] Crucian, B. E., Choukèr, A., Simpson, R. J., Mehta, S., Marshall, G., Smith,

[23] S. M., Zwart, S. R., Heer, M., Ponomarev, S., Whitmire, A., Frippiat,

[24] J. P., Douglas, G. L., Lorenzi, H., Buchheim, J. I., Makedonas, G., Ginsburg, G. S., Ott, C. M., Pierson, D. L., Krieger, S. S., … Sams, C. (2018). Immune system dysregulation during spaceflight: Potential countermeasures for deep space exploration missions. Frontiers in Immunology, 9, 1437.

[25] Cuccarolo, P., Barbieri, F., Sancandi, M., Viaggi, S., & Degan, P. (2010). Differential behaviour of normal, transformed and Fanconi's anemia lymphoblastoid cells to modeled microgravity. Journal of Biomedical Science, 17, 63.

[26] De la Torre, G. G. (2014). Cognitive neuroscience in space. Life (Basel), 4,

[27] 281–294.

[28] Demertzi, A., Van Ombergen, A., Tomilovskaya, E., Jeurissen, B., Pechenkova, E., Di Perri, C., Litvinova, L., Amico, E., Rumshiskaya, A., Rukavishnikov, I., Sijbers, J., Sinitsyn, V., Kozlovskaya, I. B., Sunaert, S., Parizel, P. M., Van de Heyning, P. H., Laureys, S., & Wuyts, F. L. (2016). Cortical reorganization in an astronaut's brain after long-duration spaceflight. Brain Structure & Function, 221, 2873–2876.

[29] Demontis, G. C., Germani, M. M., Caiani, E. G., Barravecchia, I., Passino, C., & Angeloni, D. (2017). Human pathophysiological adaptations to the space environment. Frontiers in Physiology, 8, 547.

[30] Eigenbrod, C. (2011). Drop Tower Bremen—User's guide. Zarm Drop Tower Bremen. User Mannual. http://www.zarm.uni-bremen.de/ drop-tower/downloads/

[31] Espinosa-Jeffrey, A., Nguyen, K., Kumar, S., Toshimasa, O., Hirose, R., Reue, K., Vergnes, L., Kinchen, J., & Vellis, J. D. (2016). Simulated

[32] microgravity enhances oligodendrocyte mitochondrial function and lipid metabolism. Journal of Neuroscience Research, 94, 1434–1450.

[33] Fitts, R. H., Trappe, S. W., Costill, D. L., Gallagher, P. M., Creer, A. C., Colloton, P. A., Peters, J. R., Romatowski, J. G., Bain, J. L., & Riley, D.

a. (2010). Prolonged space flight-induced alterations in the struc- ture and function of human skeletal muscle fibres. The Journal of Physiology, 588, 3567–3592.

[34] Garrett-Bakelman, F. E., Darshi, M., Green, S. J., Gur, R. C., Lin, L., Macias,

[35] B. R., McKenna, M. J., Meydan, C., Mishra, T., Nasrini, J., Piening, B. D., Rizzardi, L. F., Sharma, K., Siamwala, J. H., Taylor, L., Vitaterna,

[36] M. H., Afkarian, M., Afshinnekoo, E., Ahadi, S., … Callahan, T. F. (2019). The NASA twins study: A multidimensional analysis of a year-long human spaceflight. Science, 364, eaau8650.

[37] Goodwin, T. J., Prewett, T. L., Wolf, D. A., & Spaulding, G. F. (1993, March). Reduced shear stress: A major component in the ability of mammalian tissues to form three-dimensional assemblies in sim- ulated microgravity. Journal of Cellular Biochemistry, 51, 301–311. https://doi.org/10.1002/jcb.240510309 PMID: 8501132.

[38] Gridley, D. S., Slater, J. M., Luo-Owen, X., Rizvi, A., Chapes, S. K., Stodieck,

[39] L. S., Ferguson, V. L., & Pecaut, M. J. (2009). Spaceflight effects on T lymphocyte distribution, function and gene expression. Journal of Applied Physiology, 106, 194–202.

[40] Grimm, D., Bauer, J., Kossmehl, P., Shakibaei, M., Schöberger, J., Pickenhahn, H., Schulze-Tanzil, G., Vetter, R., Eilles, C., Paul, M., & Cogoli, A. (2002). Simulated microgravity alters differentiation and increases apoptosis in human follicular thyroid carcinoma cells. The FASEB Journal, 16, 604–606.

[41] Grimm, D., Wehland, M., Corydon, T. J., Richter, P., Prasad, B., Bauer, J., Egli, M., Kopp, S., Lebert, M., & Krüger, M. (2020). The effects of microgravity on differentiation and cell growth in stem cells and cancer stem cells. Stem Cells Translational Medicine, 9, 882–894.

[42] Grimm, D., Wehland, M., Pietsch, J., Aleshcheva, G., Wise, P., van Loon, J., Ulbrich, C., Magnusson, N. E., Infanger, M., & Bauer, J. (2014). Growing tissues in real and simulated microgravity: New meth- ods for tissue engineering. Tissue Engineering. Part B, Reviews, 20, 555–566.

[43] Grosse, J., Wehland, M., Pietsch, J., Schulz, H., Saar, K., Hübner, N., Eilles, C., Bauer, J., Abou-El-Ardat, K., Baatout, S., Ma, X., Infanger, M., Hemmersbach, R., & Grimm, D. (2012). Gravity-sensitive signal- ing drives 3-dimensional formation of

multicellular thyroid cancer spheroids. The FASEB Journal, 26, 5124–5140.

[44] Hybel, T. E., Dietrichs, D., Sahana, J., Corydon, T. J., Nassef, M. Z., Wehland, M., Krüger, M., Magnusson, N. E., Bauer, J., Utpatel, K., Infanger, M., Grimm, D., & Kopp, S. (2020). Simulated microgravity influences VEGF, MAPK, and PAM signaling in prostate cancer cells. International Journal of Molecular Sciences, 21, 1263.

[45] Kamiya, K., Ozasa, K., Akiba, S., Niwa, O., Kodama, K., Takamura, N., Zaharieva, E. K., Kimura, Y., & Wakeford, R. (2015). Long-term ef- fects of radiation exposure on health. Lancet, 386, 469–478.

[46] Keith, D., & El-Husseini, A. (2008). Excitation control: Balancing PSD-95 function at the synapse. Frontiers in Molecular Neuroscience, 1, 4.

[47] Kelly, S. E., Di Benedetto, A., Greco, A., Howard, C. M., Sollars, V. E., Primerano, D. A., Valluri, J. V., & Claudio, P. P. (2010). Rapid se- lection and proliferation of CD133+ cells from cancer cell lines: Chemotherapeutic implications. PLoS One, 5, e10035.

[48] Kirchen, M. E., O'Connor, K. M., Gruber, H. E., Sweeney, J. R., Fras, I. A., Stover, S. J., Sarmiento, A., & Marshall, G. J. (1995). Effects of mi- crogravity on bone healing in a rat fibular osteotomy model. Clinical Orthopaedics and Related Research, 318, 231–242.

[49] Konstantinova, I. V., Rykova, M. P., Lesnyak, A. T., & Antropova, E. A. (1993). Immune changes during long-duration missions. Journal of Leukocyte Biology, 54, 189–201.

[50] Koppelmans, V., Bloomberg, J. J., Mulavara, A. P., & Seidler, R. D. (2016). Brain structural plasticity with spaceflight. NPJ Microgravity, 2, 2.

[51] Kossmehl, P., Shakibaei, M., Cogoli, A., Infanger, M., Curcio, F., Schönberger, J., Eilles, C., Bauer, J., Pickenhahn, H., Schulze-Tanzil, G., Paul, M., & Grimm, D. (2003). Weightlessness induced apopto- sis in normal thyroid cells and papillary thyroid carcinoma cells via extrinsic and intrinsic pathways. Endocrinology, 144, 4172–4179.

[52] Kramer, L. A., Hasan, K. M., Stenger, M. B., Sargsyan, A., Laurie, S. S., Otto, C., Ploutz-Snyder, R. J., Marshall-Goebel, K., Riascos, R. F., & Macias, B. R. (2020). Intracranial effects of microgravity: A pro- spective longitudinal MRI study. Radiology, 295, 640–648.

[53] Kuznetsova, G. D., Gabova, A. V., Lazarev, I. E., IuV, O., KIu, O., Morozov,

a. A., Kulikov, M. A., Shchatskova, A. B., Vasil'eva, O. N., & Tomilovskaia, E. S. (2015). Frequency-temporal structure of human electroencephalogram in the condition of artificial hypogravity: Dry immersion model. Aerospace and Environmental Medicine, 49, 25–32.

[54] Lawley, J. S., Petersen, L. G., Howden, E. J., Sarma, S., Cornwell, W. K., Zhang, R., Whitworth, L. A., Williams, M. A., & Levine, B. D. (2017). Effect of gravity and microgravity on intracranial pressure. The Journal of Physiology, 595, 2115–2127.

[55] Lee, A. G., Mader, T. H., Gibson, C. R., & Tarver, W. (2017). Space flight- associated neuro-ocular syndrome. JAMA Ophthalmology, 135, 992–994.

[56] Li, J., Zhang, S., Chen, J., Du, T., Wang, Y., & Wang, Z. (2009). Modeled microgravity causes changes in the cytoskeleton and focal adhe- sions, and decreases in migration in malignant human MCF-7 cells. Protoplasma, 238, 23–33.

[57] Liao, Y., Zhang, J., Huang, Z., Xi, Y., Zhang, Q., Zhu, T., & Liu, X. (2012). Altered baseline brain activity with 72 h of simulated microgravity-

[58] -initial evidence from resting-state fMRI. PLoS One, 7, e52558 PMC3528642.

[59] Lipnicki, D. M. (2009). Baroreceptor activity potentially facilitates corti- cal inhibition in zero gravity. NeuroImage, 46, 10–11.

[60] Liu, Q., Zhou, R., Chen, S., & Tan, C. (2012). Effects of head-down bed rest on the executive functions and emotional response. PLoS One, 7, e52160.

[61] Ma, X., Pietsch, J., Wehland, M., Schulz, H., Saar, K., Hübner, N., Bauer, J., Braun, M., Schwarzwälder, A., Segerer, J., Birlem, M., Horn, A., Hemmersbach, R., Waßer, K., Grosse, J., Infanger, M., & Grimm, D. (2014). Differential gene expression profile

and altered cytokine secre- tion of thyroid cancer cells in space. The FASEB Journal, 28, 813–835.

[62] Manzey, D., & Lorenz, B. (1998). Mental performance during short-term and long-term spaceflight. Brain Research. Brain Research Reviews, 28, 215–221.

[63] Mao, X. W., Sandberg, L. B., Gridley, D. S., Herrmann, E. C., Zhang, G., Raghavan, R., Zubarev, R. A., Zhang, B., Stodieck, L. S., Ferguson,

[64] V. L., Bateman, T. A., & Pecaut, M. J. (2018). Proteomic analysis of mouse brain subjected to spaceflight. International Journal of Molecular Sciences, 20, 7.

[65] Martinez, D. A., Vailas, A. C., Vanderby, R., Jr., & Grindeland, R. E. (2007). Temporal extracellular matrix adaptations in ligament during wound healing and hindlimb unloading. American Journal of Physiology. Regulatory, Integrative and Comparative Physiology, 293, R1552–R1560.

[66] Marušič, U., Meeusen, R., Pišot, R., & Kavcic, V. (2014). The brain in micro- and hypergravity: The effects of changing gravity on the brain elec- trocortical activity. European Journal of Sport Science, 14, 813–822.

[67] Masiello, M. G., Cucina, A., Proietti, S., Palombo, A., Coluccia, P., D'Anselmi, F., Dinicola, S., Pasqualato, A., Morini, V., & Bizzarri, M. (2014). Phenotypic switch induced by simulated microgravity on MDA-MB-231 breast cancer cells. BioMed Research International, 2014, 652434.

[68] Melnik, D., Sahana, J., Corydon, T. J., Kopp, S., Nassef, M. Z., Wehland, M., Infanger, M., Grimm, D., & Krüger, M. (2020). Dexamethasone inhibits spheroid formation of thyroid cancer cells exposed to sim- ulated microgravity. Cell, 9, 367.

[69] Messerotti Benvenuti, S., Bianchin, M., & Angrilli, A. (2011). Effects of simulated microgravity on brain plasticity: A startle reflex habitua- tion study. Physiology & Behavior, 104, 503–506.

[70] Morita, H., Abe, C., & Tanaka, K. (2016). Long-term exposure to micro- gravity impairs vestibulo-cardiovascular reflex. Scientific Reports, 6, 33405.

[71] Muir, J., Judex, S., Qin, Y. X., & Rubin, C. (2011). Postural instability caused by extended bed rest is alleviated by brief daily exposure to low magnitude mechanical signals. Gait & Posture, 33, 429–435.

[72] Mukhopadhyay, S., Saha, R., Palanisamy, A., Ghosh, M., Biswas, A., Roy, S., Pal, A., Sarkar, K., & Bagh, S. (2016). A systems biology pipe- line identifies new immune and disease related molecular signa- tures and networks in human cells during microgravity exposure. Scientific Reports, 6, 25975.

[73] Nabavi, N., Khandani, A., Camirand, A., & Harrison, R. E. (2011). Effects of microgravity on osteoclast bone resorption and osteoblast cyto- skeletal organization and adhesion. Bone, 49, 965–974.

[74] Overbey, E. G., Paul, A. M., da Silveira, W. A., Tahimic, C. G. T., Reinsch,

[75] S. S., Szewczyk, N., Stanbouly, S., Wang, C., Galazka, J. M., & Mao,

[76] X. W. (2019). Mice exposed to combined chronic low-dose irradia- tion and modeled microgravity develop long-term neurological se- quelae. International Journal of Molecular Sciences, 20, 4094.

[77] Ozasa, K., Cullings, H. M., Ohishi, W., Hida, A., & Grant, E. (2019). Epidemiological studies of atomic bomb radiation at the radia- tion effects research foundation. International Journal of Radiation Biology, 95, 879–891.

[78] Parihar, V. K., Allen, B. D., Caressi, C., Kwok, S., Chu, E., Tran, K. K., Chmielewski, N. N., Giedzinski, E., Acharya, M. M., Britten, R. A., & Baulch, J. E. (2016). Cosmic radiation exposure and persistent cog- nitive dysfunction. Scientific Reports, 6, 34774.

[79] Parihar, V. K., Pasha, J., Tran, K. K., Craver, B. M., Acharya, M. M., & Limoli, C. L. (2015). Persistent changes in neuronal structure and synaptic plasticity caused by proton irradiation. Brain Structure & Function, 220, 1161–1171.

[80] Patel, Z. S., Brunstetter, T. J., Tarver, W. J., Whitmire, A. M., Zwart, S. R., Smith, S. M., & Huff, J. L. (2020). Red risks for a journey to the red planet: The highest priority human health risks for a mission to Mars. NPJ Microgravity., 6, 33.

[81] Pechenkova, E., Nosikova, I., Rumshiskaya, A., Litvinova, L., Rukavishnikov, I., Mershina, E., Sinitsyn, V., Van Ombergen, A., Jeurissen, B., Jillings, S., Laureys, S., Sijbers, J., Grishin, A., Chernikova, L., Naumov, I., Kornilova, L., Wuyts, F. L., Tomilovskaya, E., & Kozlovskaya, I. (2019). Alterations of functional brain connectivity after long-duration spaceflight as revealed by fMRI. Frontiers in Physiology, 10, 761.

[82] Pesenti, C., Navone, S. E., Guarnaccia, L., Terrasi, A., Costanza, J., Silipigni, R., Guarneri, S., Fusco, N., Fontana, L., Locatelli, M., Rampini, P., Campanella, R., Tabano, S., Miozzo, M., & Marfia, G. (2019). The genetic landscape of human glioblastoma and matched primary cancer stem cells reveals intratumour similarity and intertumour heterogeneity. Stem Cells International, 2019, 2617030.

[83] Pisanu, M. E., Noto, A., De Vitis, C., Masiello, M. G., Coluccia, P., Proietti, S., Giovagnoli, M. R., Ricci, A., Giarnieri, E., Cucina, A., Ciliberto, G., Bizzarri, M., & Mancini, R. (2014). Lung cancer stem cell lose their stemness default state after exposure to microgravity. BioMed Research International, 2014, 470253.

[84] Prasad, B., Grimm, D., Strauch, S. M., Erzinger, G. S., Corydon, T. J., Lebert, M., Magnusson, N. E., Infanger, M., Richter, P., & Krüger, M. (2020). Influence of microgravity on apoptosis in cells, tissues, and other systems in vivo and in vitro. International Journal of Molecular Sciences, 21, 9373.

[85] Preissmann, D., Leuba, G., Savary, C., Vernay, A., Kraftsik, R., Riederer, M., Schenk, F., Riederer, B. M., & Savioz, A. (2012). Increased postsynaptic density protein-95 expression in the frontal cortex of aged cognitively impaired rats. Experimental Biology and Medicine (Maywood, N.J.), 237, 1331–1340.

[86] Reschke, M. F., Bloomberg, J. J., Paloski, W. H., Mulavara, A. P., Feiveson,

a. H., & Harm, D. L. (2009). Postural reflexes, balance control, and functional mobility with long-duration head-down bed rest. Aviation, Space, and Environmental Medicine, 80, A45–A54.

[87] Roberts, D. R., Ramsey, D., Johnson, K., Kola, J., Ricci, R., Hicks, C., Borckardt, J. J., Bloomberg, J. J., Epstein, C., & George, M. S. (2010). Cerebral cortex plasticity after 90 days of bed rest: Data from TMS and fMRI. Aviation, Space & Environmental Medicine, 81, 30–40.

[88] Sabbatini, M. (2014). Sounding rockets. In European Space Agency (Ed.), ESA user guide to low gravity platforms (3rd ed.). European space agency.

[89] Sarkar, P., Sarkar, S., Ramesh, V., Kim, H., Barnes, S., Kulkarni, A., Hall, C., Wilson, B. L., Thomas, R. L., Pellis, N. R., & Ramesh, G. T. (2008). Proteomic analysis of mouse hypothalamus under simu- lated microgravity. Neurochemical Research, 33, 2335–2341.

[90] Schneider, S., Brümmer, V., Carnahan, H., Dubrowski, A., Askew, C. D., & Strüder, H. K. (2008). What happens to the brain in weightlessness? A first approach by EEG tomography. NeuroImage, 42, 1316–1323.

[91] Schwarz, R.P., Goodwin, T.J., & Wolf, D.A. Cell culture for three-dimensional modeling in rotating-wall vessels: an application of simulated micro- gravity. Journal of Tissue Culture Methods 14, 51–57 (1992).

[92] Shi, L., Tian, H., Wang, P., Li, L., Zhang, Z., Zhang, J., & Zhao, Y. (2021). Spaceflight and simulated microgravity suppresses macrophage

[93] development via altered RAS/ERK/NFκB and metabolic pathways.

[94] Cellular & Molecular Immunology, 18, 1489–1502.

[95] Shi, Z. X., Rao, W., Wang, H., Wang, N. D., Si, J. W., Zhao, J., Li, J. C., &

[96] Wang, Z. R. (2015). Modeled microgravity suppressed invasion and migration of human glioblastoma U87 cells through downregulating store-operated calcium entry. Biochemical and Biophysical Research Communications, 457, 378–384.

[97] Silvani, G., Basirun, C., Wu, H., Mehner, C., Poole, K., Bradbury, P., & Chou, (2021). A 3D-bioprinted vascularized glioblastoma-on-a-Chip for studying the impact of simulated microgravity as a NovelPre-clinical approach in brain tumor therapy. Advances in Therapy, 4, 2100106.

[98] Smith, S. M., & Heer, M. (2002). Calcium and bone metabolism during space flight. Nutrition, 18, 849–852.

[99] Sonnenfeld, G., Mandel, A. D., Konstantinova, I. V., Berry, W. D., Taylor,

[100] G. R., Lesnyak, A. T., Fuchs, B. B., & Rakhmilevich, A. L. (1992). Spaceflight alters immune cell function and distribution. Journal of Applied Physiology, 73, 191S–195S.

[101] Stowe, R. P., Sams, C. F., & Pierson, D. L. (2011). Adrenocortical and im- mune responses following short- and long-duration spaceflight. Aviation, Space, and Environmental Medicine, 82, 627–634.

[102] Strube, F., Infanger, M., Dietz, C., Romswinkel, A., & Kraus, A. (2019). Short-term effects of simulated microgravity on morphology and gene expression in human breast cancer cells. Physiology International, 106, 311–322.

[103] Takeda, M., Magaki, T., Okazaki, T., Kawahara, Y., Manabe, T., Yuge, L., & Kurisu, K. (2009). Effects of simulated microgravity on prolifer- ation and chemosensitivity in malignant glioma cells. Neuroscience Letters, 463, 54–59.

[104] Topal, U., & Zamur, C. (2021). Microgravity, stem cells, and cancer: A new Hope for cancer treatment. Stem Cells International, 2021, 5566872. Ulbrich, C., Wehland, M., Pietsch, J., Aleshcheva, G., Wise, P., van Loon, J., Magnusson, N., Infanger, M., Grosse, J., Eilles, C., Sundaresan,

[105] A., & Grimm, D. (2014). The impact of simulated and real micro- gravity on bone cells and mesenchymal stem cells. BioMed Research International, 2014, 928507.

[106] Uva, B. M., Masini, M. A., Sturla, M., Prato, P., Passalacqua, M., Giuliani, M., Tagliafierro, G., & Strollo, F. (2002). Clinorotation-induced weightlessness influences the cytoskeleton of glial cells in culture. Brain Research, 934, 132–139.

[107] Vaitl, D., Gruppe, H., Stark, R., & Pössel, P. (1996). Simulated micro- gravity and cortical inhibition: A study of the hemodynamic-brain interaction. Biological Psychology, 42, 87–103.

[108] Van Ombergen, A., Laureys, S., Sunaert, S., Tomilovskaya, E., Parizel,

[109] P. M., & Wuyts, F. L. (2017). Spaceflight-induced neuroplasticity

[110] in humans as measured by MRI: What do we know so far? NPJ Microgravity, 3, 2.

[111] Vassy, J., Portet, S., Beil, M., Millot, G., Fauvel-Lafève, F., Gasset, G., & Schoevaert, D. (2003). Weightlessness acts on human breast can- cer cell line MCF-7. Advances in Space Research, 32, 1595–1603.

[112] Vidyasekar, P., Shyamsunder, P., Arun, R., Santhakumar, R., Kapadia, N. K., Kumar, R., & Verma, R. S. (2015). Genome wide expression pro- filing of cancer cell lines cultured in microgravity reveals significant dysregulation of cell cycle and MicroRNA gene networks. PLoS One, 10, e0135958.

[113] Von Kampen, P., Kaczmarczik, U., & Rath, H. J. (2006). The new drop tower catapult system. Acta Astronautica, 59, 278–283.

[114] Wake, H., Moorhouse, A. J., Miyamoto, A., & Nabekura, J. (2013). Microglia: Actively surveying and shaping neuronal circuit struc- ture and function. Trends in Neurosciences, 36, 209–217.

[115] Wang, X., Du, J., Wang, D., Zeng, F., Wei, Y., Wang, F., Feng, C., Li, N., Dai, R., Deng, Y., Quan, Z., & Qing, H. (2016). Effects of simulated microgravity on human brain nervous tissue. Neuroscience Letters, 627, 199–204.

[116] Weller, M., van den Bent, M., Tonn, J. C., Stupp, R., Preusser, M., Cohen- Jonathan-Moyal, E., Henriksson, R., Le Rhun, E., Balana, C., Chinot, O., Bendszus, M., Reijneveld, J. C., Dhermain, F., French, P., Marosi, C., Watts, C., Oberg, I., Pilkington, G., Baumert, B. G.,

[117] … Wick, W. (2017). European Association for Neuro-Oncology (EANO) guideline on the diagnosis and treatment of adult astrocytic and oligodendroglial gliomas. The Lancet Oncology, 18, e315–e329.

[118] Wipfler, K., Cornish, A. S., & Guda, C. (2018). Comparative molecular characterization of typical and exceptional responders in glioblas- toma. Oncotarget, 9, 28421–28433.

[119] Wolfe, J. W., & Rummel, J. D. (1992). Long-term effects of micrograv- ity and

possible countermeasures. Advances in Space Research, 12, 281–284.

[120] Yuge, L., Sasaki, A., Kawahara, Y., Wu, S. L., Matsumoto, M., Manabe, T., Kajiume, T., Takeda, M., Magaki, T., Takahashi, T., Kurisu, K., & Matsumoto, M. (2011). Simulated microgravity maintains the undifferentiated state and enhances the neural repair potential of bone marrow stromal cells. Stem Cells and Development, 20, 893–900.

[121] Zhao, J., Ma, H., Wu, L., Cao, L., Yang, Q., Dong, H., Wang, Z., Ma, J., & Li,

[122] Z. (2017). The influence of simulated microgravity on proliferation and apoptosis in U251 glioma cells. In Vitro Cellular & Developmental Biology-Animal, 53, 744–751.

[123] Zhu, M., Jin, X. W., Wu, B. Y., Nie, J. L., & Li, Y. H. (2014, August 7).

[124] Effects of simulated weightlessness on cellular morphology and biological characteristics of cell lines SGC-7901 and HFE-145. Genetics and Molecular Research, 13(3), 6060–6069. https://doi.org/10.4238/2014.August.7.20 PMID: 25117363.