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Research Article

Geriatric Space Travel©

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Abstract

The world community continues to move towards exploring the solar system, with exploration of our immediate solar system aimed at establishing intra-planetary colonies, first perhaps on our nearest Earth neighbour Mars. Long haul and intergenerational space flight, with intra- and perhaps extra-planetary colonisation, at the current level of technology, will probably create the need for geriatric space travel.

Humans are uniquely adapted to a live, survive and thrive in Earth gravity (1g) of approximately 9.8m^2. When humans move beyond this gravity and the Earth's protective gravitational field, human growth, development and physiology is impacted. This brings to the forefront two main areas of consideration: multi-morbidity and increasingly complex care needs of an active geriatric crew, whose skills, academia and practical knowledge may be required for longer, and more enduring working lives, and the physiological hostility of altered gravity environments.

Whilst aging on Earth is a complex topic; altered gravity environments will bring even greater challenges. Bodily systems known to be affected by altered gravity environments include the immune, cardio-vascular and muscular-skeletal systems. Gross affects on these systems have been catalogued over the years; the most notable being rapid onset of osteopenia and osteoporosis, even after relatively short exposure to altered gravity environments of two weeks. Newer areas of study of the effects of altered gravity have broadened to include infection susceptibility and disruptions to the gastrointestinal-pulmonary and gastrointestinal-skin axes. Nutritional changes caused by gastrointestinal microbiome imbalances can affect both the uptake of nutrients as well as medications, with possible impacts on cellular operations and perhaps cognition.

In the altered gravity environment those individuals genetically predisposed to certain diseases may be at risk of accelerated onset of cognitive decline, immunological and physiological changes. This paper explores some of the known physiological stresses caused by altered gravity environments, highlighting the possibly of disease and aging insults that may be experienced by the geriatric astronaut.

Keywords: Geriatric, microgravity, altered gravity environments, long haul space flight, intergenerational space flight, intra-planetary colonisation

Introduction

Human or Earth orientated beings struggle in altered- or micro-gravity (*µg*) [1-3]. It is apparent that human cells are uniquely bound to the Earth gravity of 9.8 m^2 (1g) [4-6]. When humans are removed from 1g experience shows that almost all physiological systems are affected. Such data that has been collected over the years from various space programs: The Russian Soyuz and MIR missions, The International Space Station (ISS), Skylab and from relatively short haul shuttle resupply and satellite launch missions [7]. Mission data confirms that even minute changes in gravity can have significant effects on human health. To appreciate these concepts, ISS gravity is 89% of 1g but effective gravity is 0, hence even short trips of 2 weeks create appreciable measurable bony changes on the osteoporotic continuum in astronauts [8,9]. These altered gravity impacts have been described affecting the musculoskeletal, cardiovascular and immunological systems and are hypothesized to be the expression of cellular change [10-13]. If short exposure to altered gravity creates physiological changes, it can be assumed that biological protection will be needed for humans in this hostile environment, with particular consideration given to longer journeys or colonisation [14,15].

Missions to the ISS for example, are mere 'hops', with respect to distance and time, when compared to journeys to the outer planets of our solar system or beyond. These journeys require long haul/inter-generational space flight based on current rocket propellant technology. Problems caused by the altered gravity environment and its influence on the human body will not abate with colonisation of the Earth's Moon or our nearest planet Mars [16,17]. Appreciating the gravity of the Moon is approximately 0.017% of 1g and Mars 0.028%-0.038% of 1g, the gravitational influence on human living systems and the evolution of their molecules on Earth, it is reasonable to predict that any colonisation outside of 1g will be extremely challenging for the human species survive and thrive [18-20].

Aging on Earth, as a testament to ongoing medical science, has seen healthcare dominated by individuals with multiple comorbidities and complex care needs, resulting in significant challenges for practitioners and the community overall [21]. Mental and behavioural conditions (including anxiety, depression and mood disorders), musculoskeletal (including arthritis), respiratory (including asthma) and endocrine and metabolic conditions (including diabetes) were the most common health concerns managed by general practitioners in Australia in 2021, consistent with most developed Western countries [22, 23] It would be expected that the same conditions, especially those which are innate to the aging human, would be encountered with long haul and intergenerational space flights.

Adding complexity is the growing knowledge of the human skin- and gut- microbiomes and the various axes the gastrointestinal tract contributes. The gastrointestinal-skin axis plays an important role in immune and cognitive health; whilst the gastrointestinal-pulmonary axis sees mutual support of both systems for healthy nutritional and immunological states [24-29]. There is increasing evidence that gut microbiome is both genetically and environmentally determined, as changes to an individual's gut microbiome has been observed in a confined habitats, becoming 'generic' in nature across all inhabitants [30-32]. This can contribute to mitochondrial dysfunction and an independent effect on the human immune system, with downstream effects on nutrition and medicine uptake, as well as impacting on overall healing capacity [30-32].

The Earth's gravitational field protects humans and mammals from the radiation innate in space. There are arguments for and against the current level of space travel affecting or inducing cancer, with some researchers advocating the use of alternative medicines so that space travelers may 'grow' future treatments [33-35]. Increased cellular turnover observed in bacteria and mammalian cells (e.g. osteoblasts) brings into question broader aging and cancer considerations; cells affected by the environment of altered gravity may also be provoked by increased radiation exposure [36-38]. This perhaps couples poorly with the possibility of weak B-Cell surveillance creating a form of immuno-suppression, worsened by their misfunction due to changes in lymphatic fluid dynamics [36-38].

There is of course, with any aging population, the inevitably to consider palliative care requirements in an off-Earth space setting. Unlike older populations on Earth where the conversations about resource allocation is not one currently considered (in most Western nations), this may become an issue which future space bound clinicians may be forced to discuss [39].

Conditions and diseases that are experienced by older populations on Earth are expected to occur in the same rate in space based aging populations [40, 41]. Without a resolution to create gravity that mimics Earth's, longer space flight scenarios are anticipated to have greater and ongoing impacts on the human body. This discussion gives consideration to altered gravity environments impact on immunological responses, changes to bacterial and viral pathogenesis (with an increased infection risk) and the increased hazard of oestopenia and osteoporosis (occurring at a younger age than which is experienced on Earth), as well as morphological cardio-vascular changes, an older person's potential for cognitive changes, perhaps made worse, by the overall effect on and changes to, the gut microbiome alterations observed in confined habitats. This discussion by no means considers all the issues, both known and predicted, but aims to open the conversation about the challenges of geriatric space travel, which may create, for the geriatric astronaut, the possibly of diminishing health returns in a clinical environment of limited or scarce resources [42-44].

The physiological effects of altered gravity environments

The physiological effects of altered gravity environments on the human body are wide and varied. They include ocular-vestibular changes, blood clotting and wound healing dysfunction, increased cellular turnover and the more widely appreciated cardio-vascular and musculo-skeletal changes [45-47]. There is good evidence to support gene dysregulation, immune dysfunction and disturbances in cellular and immune signaling as the contributors to some of these effects [48]. These effects may or may not be coupled with increased radiation exposure, from which the Earth's gravitational field currently provides humans with protection [49, 50]. In addition, there is the interplay between radiation, altered gravity environments and DNA damage, affecting DNA repair mechanisms. Our current knowledge enables predictions of increased cancer risk, perhaps aided by dysfunctional or lasped B-Cell surveillance [51-55].

Apoptosis is not spared in altered gravity; the cellular processes may slow or be nonresponsive due to a loss of vital chemical signals that control this process [56-60]. Cancer in an aging space population may present differently as to a clinician's expectations and experience on Earth. Primary presentation may be a relatively short period of time before either tissue invasiveness or metastases. Cancer cell morphology may not be recognisable due to cellular morphological changes and biochemical markers may not be encountered or recognisable due to changes in protein expression or structure. Surveillance and monitoring tools may not be of the same value as on Earth and certain proteins may appear in unexpected volume or at an unexpected timeline for the disease [57-62]. Changes to three dimensional (3D) molecular structures may impact enzymatic and immune functions. Especially if coupled with nutritional changes (e.g. loss of vital nutrient uptake) due to the impact of a shared generic gastrointestinal microbiome, affecting eons of genetically determined and individually curated microbiomes [63-67]. And there is the consideration that genetic predisposition for some diseases, which might not 'activate' in 1g, may become more prevalent in altered gravity environments,

There are ocular-vestibular and proprioception changes, each sense becoming more disordered the longer the journey in altered gravity [68-72]. Fluid dynamics in altered gravity environments create vision changes thought to be the result of a conformational change in shape of the eyeball and/all some occlusion of the optic nerve. With conformational changes of the eyeball, radiation exposure and altered gravity effect on the ocular-vestibular apparatus results in motion sickness arising from the middle ear. With continued exposure to altered gravity, gravity and proprioception feedback become more disconnected. The vestibular system becomes further deconditioned causing further motion sickness, persisting when astronauts return to 1g. Some of the vision changes can be beneficial, i.e. correct vision, alternatively the new fluid dynamics experienced can also create vision problems, such as myopia and presbyopia.

For astronauts their peak physical condition is vital, however a long known side effect of altered gravity environments is the rapid onset of osteopenia and corresponding osteoporosis, which is not abated by exercise. Studies show that effect on oestoblasts can occur in as little as two weeks and persist for over 12 months on return to 1g. Further considerations must be given to peri- and post-menopausal women and other individuals genetically prone to such musculo-skeletal disorders when considering crews for long haul space flight.

Human physiology is uniquely adapted for Earth's gravity, the further humans venture into the altered gravity environments, the more health and welfare issues will appear. Research indicates that management challenges, resource and medicine limitations will compound the clinical decision making processes. There is a high probability that new and novel medicines and methodologies will be needed to keep geriatric space travelers healthy for their missions. This paper aims to highlight four areas that space scientists have gathered some data on the impact of altered gravity [73]. It is important to note that the data thus far collected may or may not extrapolate to extended altered gravity environments and/or intergenerational space flight.

Musculo-skeletal changes in altered gravity environments

During space flight (such as short haul or ISS terms) weight-bearing bones lose approximately 1 per cent of their mineralized density per month with an accompanying loss of muscle mass (bulk) [74, 75]. There is a faster decline in altered gravity environments without exercise, leading to the conclusion that the resistance of gravity is required to ensure bone health and muscle bulk [74, 75]. Some astronauts reviewed post ISS and shuttle missions did not recover their pre-flight bone density, after return from their missions, within 12 months of exposure to 1g [76, 77].

There is evidence that the disordered ratio between the action of the oesteoblasts and osteoclasts, along with other mechanisms not yet recognized, lead to bone demineralization, most notably in the weight bearing bones of the human body and even vigorously scheduled exercise does not completely abate the issues [78,79]. Ongoing research has not defined the reason for the rapid change in osteocyte behavior [80-85]. Spaceflight induced bone and tissue changes in peri- and post- menopause woman increase the risk of diminishing bone quality and fractures [86-88]. Modern methods of management rely on the balancing ratio of reabsorbing of bone and its minerals, and medications (i.e. biphosophonates) have been used as bone stabilization medications on Earth for many years. However this medication may not be suitable for space flight due to the increased risk of renal calculi formation, and new alternatives are not yet tested in altered gravity environments [89-92]. Another consideration, apart from the trauma caused by fracture, including the difficulties of surgical intervention in altered gravity environments: blood does not clot, wounds heal poorly, the risk of infection is higher (common benign bacteria change their pathogenesis in microgravity) and pain management is difficult to achieve [93].

Altered gravity environment's effect on the cardio-vascular systems

The effect of altered gravity on the heart has long been catalogued; however it is perhaps now with our increased knowledge of the heart that the view of these changes has become more appreciated [94, 95]. The heart changes in size and the chambers change their overall capacity, becoming more the morphology akin to that of a long term sufferer of poorly controlled blood pressure [96-100]. The challenge in altered gravity environments is to maintain the cardiovascular health of astronauts, not only in the shorter term, but also in the longer term with consideration of long haul space flight, where radiation may also have an independent and as yet not catalogued effect [101,102]. This is more complicated when modern pharmacological management of cardiac disease are considered, as the availability of medications and their bioavailability are areas of interest for flight surgeons, particularly if gut microbiome changes impact on the bioavailability [103]. Reactive Oxygen Species (ROS) is increased in altered gravity environments and has an influence on the genetic expression of cardiac and other cells [97-100]. Downstream effects of the change in cardiac morphology concern the heart's compromised 'pumping' ability, causing the development of splenic and upper body congestion, renal failure and lymphatic fluid drainage changes [104,105]. Lymphatic flow is normally supported by both cardiac output and the body's various muscle pumps. The changes to lymphatic fluid dynamics are a double consequence of lack of cardiac output strength as well as change in fluid dynamics in altered gravity. Changes in the lymphatic flow has an obstructive effect on antibodies, peptides, immune complexes, growth factors and all things in the human body that use the lymphatic system as a metaphoric "highway". Unfortunately for humans we do not have the baroreptors of giraffes [106]. Eventually cardiac changes

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lead to baroreceptor dysfunction and blood pressure changes [107-109]. The body's ability to regulate blood pressure deteriorates the longer a person spends in an altered gravity environment; clinically resulting in light-headedness and fainting (on return to 1g), signaling a physical and physiological change in the receptor behaviour [108-110]. These cardiac effects may become complicated medical risks for the geriatric astronaut.

Cognitive changes

Mood disorders in the older patient can have a severe affect on their interactions, insight, contribution and maintenance of relationships [111-113]. The acquired skill and knowledge held by the geriatric astronauts, who may still be working at full capacity in their work team environment, will be challenged further by enclosed spaceship environments, where changes to cognition may cause a range of unanticipated issues [114,115]. Like all patients, physiological causes for changes in mood and social interaction would need to be ruled out/treated and any correctable nutrient, endocrine or metabolic contribution, including gastrointestinal microbiome imbalance affecting uptake of nutrients and/or medications, would need to be corrected [116-119]. Mood disorders, however, are a complex condition, which often reaches beyond nutrition and physiological causes. Clinicians will require tools to maintain their patient's activities and contributions. It may be the case that space clinicians will require sub-specialty skill sets to keep older valued members of the mission team in peak condition [120-122].

In the space environment a change in gastrointestinal microbiome (from individual to generic) can have implications for the uptake of nutrients, and one such nutrient, Vitamin D, is cardinal for healthy minds and the immune system in older patients and therefore older astronauts [4, 123-127]. There are age related changes which occur to the human anterior pituitary's ACTH secretion, noting that ACTH is an important component of the hypothalamic-pituitary-adrenal axis. As a chemical signaler, ACTH's principal effects are increased production and release of cortisol and androgens, stimulating the cortex and medulla of the adrenal gland as well as a role in the maintenance of the circadian rhythm in many organisms [128-134]. ACTH is also produced in response to biological stress (along with its precursor corticotrophin-releasing hormone from the hypothalamus). Biological changes to ACTH either by disease, age related changes or radiation and the high stress environment of space flight could contribute to potential dysfunction, and in this could be catastrophic not only to the individual but the entire crew [135-137].

There is an overlay between the neuro-immune status of an individual and the onset and progression of neurodegenerative disorders and disease [138-141]. The aging process in these cells may be accelerated or decelerated in altered gravity environments; the consequence of this mechanism of aging is not yet explored in altered gravity [142,143]. Treatment regimens may need to include pharmacological, psychological, psychiatric or physical, such as SAD treatment with UV radiation [144-146]. Cognitive decline may be attributable to change in cerebral blood flow/changed fluid dynamics due to altered gravity effects on the cardio-vascular system [157-160]. However if the base ingredient, medication or other treatment options are not available, treating clinicians may be quite challenged to manage excesses or deficiencies contributing to any mood disorder or cognitive decline. Cognitive decline is a condition that clinicians grapple with on Earth, in altered gravity environments it may be more perfuse and diffuse, with the potential to significantly impact on the mission parameters and safety [161-163]. Early studies appear to indicate a range of brain cells are adversely and perhaps selectively affected by altered gravity environments, as well as exposure to radiation [164,165]. On Earth this radiation is kept at bay by the Earth's gravitational field, in space there is no such protection that our current collective level of technology can offer.

A topic not often broached in modern Western medicine is resource allocation. In the finite environment that space missions present, along with forecasted limited resources, scenarios surrounding rationing of medicine and treatments may be something that requires external (to medicine) protocols and procedures [147-149]. The cardinal question of value of single individual and that of the "greater good" is not a comfortable discussion for modern day clinicians but may be a pragmatic consequence of resource management in space exploration [150-152]. Considerations that are beyond our current technology, such as hibernation chambers, enforced sleep or gross disturbances to the circadian rhythm, may require intensive investigation before they are implemented due to the known effects these may have on mood and cognitive functions [93, 99-100, 153-156].

Immuno-suppression and infection

There is a complex picture of acquired immuno-suppression and poor wound healing experienced in altered gravity environments. The increased infection risk, aided and abetted by the changes in the bacterial growth rates (recorded to be increased up 4-6 times faster on the ISS when compared to Earth's 1g) are accompanied by morphological, behavioural and virulence changes [4, 47, 166-171]. Friendly commensals of the skin microbiome can morph to into an organism of pathogenesis in a very short period of time [172,173].

There also appears to be a poorly understood direct insult on the human immune system, creating T-Cell dysfunction that continues up to 12 months on return to 1g [174-177]. This has been considered as a cause for the reactivation of latent infections, such as *H. simplex*, experienced in space flight [178,179]. It is now known that altered gravity environments have an influence on gene regulation; however to what extend these impacts on both the immune system, bacterial and viral behaviour is not yet clear [180-182]. The affect of altered gravity environments on apoptosis, programmed cell death, may or may contribute to cancerous growths and affect the mechanisms of apoptosis [183,184].

Altered gravity environments impact on gene regulation and may affect cellular and molecular signaling, hindered by the changes in fluid dynamics and pseudo obstruction to lymphatic flow

[185,186]. There is also consideration for the changes to the three dimensional molecular structure of immunoglobulin's perhaps losing the 'lock and key' specificity [4, 187]. The interrupted fluid dynamics of the lymphatic system lead to a suffused upper body which is resistant to diuretic treatments [188]. Whilst endrocrine dysfunction is not well catalogued, it is noted that insulin secretion demonstrates changed dynamics, causing an independent immuno-suppressive effect [189, 190].

B-Cells have demonstrated changes in their surveillance efficiencies and this may be due to the effect of altered gravity on the lymphatic system or changes to fluid dynamics within the lymph system [11, 191-194]. T-Cells, it is presumed, may take over some of the immunological duties, leading to inflammatory cascades, which in itself is thought to promote early aging [195-197]. Evidence for this may lie in the rise of inflammatory makers in other mammals in simulated altered gravity environments, with corresponding inflammatory issues and increased cardiovascular risk [198-200].

The spectra of rapid growth rate, behavioural changes and increased virulence of bacterial and viral pathogens, along with dysfunctional T-Cells and suppressed B-Cells lead inevitability to a situation of immuno-suppression with increased infection risk and rapid antimicrobial resistance [4, 201-203]. Antibiotics unfortunately do not have the same efficiency as the do in 1g, increased bacterial and viral replication lead to rapid, short generational timeframes and an effective resistance [4, 204-208]. A concern for future scientists and physicians may well be the reactivation of viral infections, including SARS-Co-V2, within the enclosed environment of a space ship [4, 205]. Finally, there is the threat of new and exotic diseases, pathogens and life forms not yet imagined, and that for which we are not yet prepared to encounter [4, 152].

Conclusion

Space travel is no doubt one of humankind's greatest adventures; to reach the outer solar system and beyond with our current propellants and technology it is predicted that space flight will progress to long haul as well as intergenerational flights and . Crews may well be required to work into older age, as part of mission teams. Evident from the planetary population's brief foray into altered gravity environments, growth, development and aging in space will present major challenges to the human species survival in an innately hostile environment.

Threats to humans surviving and thriving will come from a multiple of fronts, such as diseases and syndromes associated with aging, nutritional maintenance for optimal functioning, immune system senescence, post-menopausal changes and increase risk of diseases (i.e. osteoporosis) and cancers (i.e. breast cancer). Changes to DNA repair mechanisms, immune signally and responses, as well as the potential for reactivation of latent diseases (i.e. *H. simplex* infections) are all omnipotent health risk factors. Aging presents increased challenges for the clinicians working in space who may be required to ration limited resources, medications and treatment options. In short, the much needed skills of a specialist Geriatrician may well be the principle specialty, for those doctors wishing to contribute to human space exploration.

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References

1. Sekiguchi C. (1994) Issues of health care under weightlessness. *Acta Physiol Scand Suppl*. 616:89-97.
2. Kandarpa K, Schneider V, Ganapathy K. (2019) Human health during space travel: An overview. *Neurol. India*. 67:S176–S181.
3. Ilyin EA, Oganov VS. (1989) Microgravity and musculoskeletal system of mammals. *Adv Space Res*. 9:11-9.
4. Caswell G, Eshelby B. (2022) Skin microbiome considerations for long haul space flights. F*ront Cell Dev Biol*. 10:956432.
5. Hart DA. Homo sapie (2023) ns-A Species Not Designed for Space Flight: Health Risks in Low Earth Orbit and Beyond, Including Potential Risks When Traveling beyond the Geomagnetic Field of Earth. *Life* (Basel). 13:757.
6. Gravity https://www.ga.gov.au/scientific-topics/disciplines/geophysics/gravity accessed November 12th 2023.
7. Stevens AH, Kobs Nawotniak SE, Garry WB, Payler SJ, Brady AL, et al. (2019) Tactical scientific decision-making during crewed astrobiology Mars missions. *Astrobiology*. 19:369–386.
8. Meer E, Grob S, Antonsen EL, Sawyer A. (2023) Ocular conditions and injuries, detection and management in spaceflight. *NPJ Microgravity*. 9:37.
9. Bonanni R, Cariati I, Marini M, Tarantino U, Tancredi V. (2023) Microgravity and Musculoskeletal Health: What Strategies Should Be Used for a Great Challenge? *Life* (Basel). 13:1423.
10. Mehta SK, Laudenslager ML, Stowe RP, Crucian BE, Sams CF, et al. (2014) Multiple latent viruses reactivate in astronauts during Space Shuttle missions. *Brain Behav Immun*. 210-7.
11. Kolev OI, Clement G, Reschke MF. (2023) Astronauts eye-head coordination dysfunction over the course of twenty space shuttle flights. *J Vestib Res*. 33:313-324.
12. Zayzafoon M, Meyers VE, McDonald JM. (2005) Microgravity: the immune response and bone. *Immunol Rev*. 208:267-80.
13. Tanaka K, Nishimura N, Kawai Y. (2017) Adaptation to microgravity, deconditioning, and countermeasures. *J. Physiol. Sci.* 67:271–281.
14. Sihver L, Mortazavi SM J. (2021) Biological Protection in Deep Space Missions. *J. Biomed. Phys. Eng*. 11:663-674.
15. H Winkler L. (2023) Human Physiological Limitations to Long-Term Spaceflight and Living in Space. *Aerosp Med Hum Perform*. 94:444-456.
16. Patel ZS, Brunstetter TJ, Tarver WJ, Whitmire AM, Zwart SR et al. (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.
17. Afshinnekoo E, Scott RT, MacKay MJ, Pariset E, Cekanaviciute E, et al. (2020) Fundamental Biological Features of Spaceflight: Advancing

the Field to Enable Deep-Space Exploration. *Cell.* 183:1162-1184.

18. Adamopoulos K, Koutsouris D, Zaravinos A, Lambrou GI. (2021) Gravitational Influence on Human Living Systems and the Evolution of Species on Earth. *Molecules.* 26:2784.

19. Afshinnekoo E, Scott RT, MacKay MJ, Pariset E, Cekanaviciute E, et al. (2020) Fundamental Biological Features of Spaceflight: Advancing the Field to Enable Deep-Space Exploration. *Cell.* 183:1162-1184.

20. Mahmud MR, Akter S, Tamanna SK, Mazumder L, Esti IZ, et al. (2022) Impact of gut microbiome on skin health: gut-skin axis observed through the lenses of therapeutics and skin diseases. *Gut Microbes.* 14:2096995.

21. Harrison C and Siriwardena A. (2018) 'Multimorbidity: editorial *Australian Journal of General Practice*, 47:7.

22. OECD (Organisation for Economic Co-operation and Development) (2021) OECD website, accessed 14th November 2023.

23. Peterson LE, Cucinotta FA. (1999) Monte Carlo mixture model of lifetime cancer incidence risk from radiation exposure on shuttle and international space station. *Mutat Res*. 430:327-35.

24. Sinha S, Lin G, Ferenczi K. (2021) The skin microbiome and the gut-skin axis. *Clin Dermatol.* 39:829-839.

25. Raftery AL, Tsantikos E, Harris NL, Hibbs ML. (2020) Links Between Inflammatory Bowel Disease and Chronic Obstructive Pulmonary Disease. *Front Immunol.* 11:2144.

26. Lee M, Chang EB. (2021) Inflammatory Bowel Diseases (IBD) and the Microbiome-Searching the Crime Scene for Clues. Gastroenterology. 160:524-537.

27. Wypych TP, Wickramasinghe LC, Marsland BJ. (2019) The influence of the microbiome on respiratory health. *Nat Immunol.* 20:1279-1290.

28. Fabbrizzi A, Amedei A, Lavorini F, Renda T, Fontana G. (2019) The lung microbiome: clinical and therapeutic implications. *Intern Emerg Med.* 14:1241-1250.

29. Nguyen HP, Tran PH, Kim KS. Yang SG. (2021) The effects of real and simulated microgravity on cellular mitochondrial function. *NPJ Microgravity* 7:44 .

30. Iwase S, Nishimura N, Tanaka K, Mano T. (2020). Effects of Microgravity on Human Physiology. IntechOpen.

31. Indo HP, Majima HJ, Terada M, Suenaga S, Tomita K, Yamada S, Higashibata A, Ishioka N, Kanekura T, Nonaka I, Hawkins CL, Davies MJ, Clair DK, Mukai C. Changes in mitochondrial homeostasis and redox status in astronauts following long stays in space. Sci Rep. 2016 Dec 16;6:39015. doi: 10.1038/srep39015. Erratum in: *Sci Rep.* 2020 Apr 20;10(1):6910. PMID: 27982062; PMCID: PMC5159838.

32. da Silveira WA, Fazelinia H, Rosenthal SB, Laiakis EC, Kim MS, et al. (2020) Comprehensive Multi-omics Analysis Reveals Mitochondrial Stress as a Central Biological Hub for Spaceflight Impact. *Cell.* 183:1185-1201.e20.

33. AMA (Australian Medical Association) (2021), AMA website, accessed 14th November 2023.

34. PDQ Integrative, Alternative, and Complementary Therapies Editorial Board. Medicinal Mushrooms (PDQ®): Health Professional Version. 2023 Jan 13. In: PDQ *Cancer Information Summaries* [Internet]. Bethesda (MD): National Cancer Institute (US).

35. Restier-Verlet J, El-Nachef L, Ferlazzo ML, Al-Choboq J, Granzotto A, et al. (2021) Radiation on Earth or in Space: What Does It Change? *Int J Mol Sci.* 22:3739.

36. Tan S, Tran V, Stretton B, Gupta A, Kovoor J, et al. (2023) The Final Frontier: Palliative Care in Space is an Inevitability. *J Palliat Care.* 38:405-406.

37. Bradbury P, Wu H, Choi JU, Rowan AE, Zhang H, et al. (2020) Modeling the Impact of Microgravity at the Cellular Level: Implications for Human Disease. *Front Cell Dev Biol.* 8:96.

38. Liao L, Schneider KM, Galvez EJC, Frissen M, Marschall HU, et al. (2019) Intestinal dysbiosis augments liver disease progression via NLRP3 in a murine model of primary sclerosing cholangitis. *Gut.* 68:1477-1492.

39. Tan S, Tran V, Stretton B, Gupta A, Kovoor J, et al. (2023) The Final Frontier: Palliative Care in Space is an Inevitability. *J Palliat Care.* 38:405-406.

40. Stratmann, H. (2016). Microgravity and the Human Body. In: Using Medicine in Science Fiction. Science and Fiction. Springer, Cham.

41. Holick MF. (1999) Perspective on the consequences of short- and long-duration space flight on human physiology. *Life Support Biosph Sci.* 6:19-27.

42. Shanmugarajan S, Zhang Y, Moreno-Villanueva M, Clanton R, Rohde LH, et al. (2017) Combined Effects of Simulated Microgravity and Radiation Exposure on Osteoclast Cell Fusion. *Int J Mol Sci.* 18:2443.

43. Smith JK. (2020) Osteoclasts and Microgravity. *Life* (Basel). 10:207.

44. Wang H, Gao L, Chen X, Zhang C. (2022) Study on mass transfer in the bone lacunar-canalicular system under different gravity fields. *J Bone Miner Metab.* 40940-950.

45. Saveko A, Bekreneva M, Ponomarev I, Zelenskaya I, Riabova A, et al. (2023) Impact of different ground-based microgravity models on human sensorimotor system. *Front Physiol.* 14:1085545.

46. Kim DS, Vaquer S, Mazzolai L, Roberts LN, Pavela J, et al. (2021) The effect of microgravity on the human venous system and blood coagulation: a systematic review. *Exp Physiol.* 106:1149-1158.

47. Radstake WE, Gautam K, Miranda S, Vermeesen R, Tabury K, et al. (2023) The Effects of Combined Exposure to Simulated Microgravity, Ionizing Radiation, and Cortisol on the In Vitro Wound Healing Process. *Cells.* 12:246.

48. Sahana J, Cortés-Sánchez JL, Sandt V, Melnik D, Corydon TJ, et al. (2023) Long-Term Simulation of Microgravity Induces Changes in Gene Expression in Breast Cancer Cells. *Int J Mol* Sci.24:1181.

49. Kawasaki K, Rekhtman N, Quintanal-Villalonga Á, Rudin CM. (2023) Neuroendocrine neoplasms of the lung and gastrointestinal system: convergent biology and a path to better therapies. *Nat Rev Clin Onco*l. 20:16-32.

50. Corydon TJ, Schulz H, Richter P, Strauch SM, Böhmer M, et al. (2023) Current Knowledge about the Impact of Microgravity on Gene Regulation. *Cells.* 12:1043.

51. Moreno-Villanueva M, Wong M, Lu T, Zhang Y, Wu H. (2017) Interplay of space radiation and microgravity in DNA damage and DNA damage response. *NPJ Microgravity.* 3:14.

52. Zhao L, Zhang G, Tang A, Huang B, Mi D. (2023) Microgravity alters the expressions of DNA repair genes and their regulatory miRNAs

in space-flown Caenorhabditis elegans. *Life Sci Space Res (Amst)*. 37:25-38.

53. Yatagai F, Honma M, Dohmae N, Ishioka N. (2019) Biological effects of space environmental factors: A possible interaction between space radiation and microgravity. *Life Sci Space Res* (Amst).20:113-123.

54. Guo Z, Zhou G, Hu W. (2022) Carcinogenesis induced by space radiation: A systematic review. Neoplasia. 32:100828.

55. Prasad B, Grimm D, Strauch SM, Erzinger GS, Corydon TJ, et al. (2020) Influence of Microgravity on Apoptosis in Cells, Tissues, and Other Systems In Vivo and In Vitro. *Int J Mol Sci.* 21:9373.

56. Willey JS, Britten RA, Blaber E, Tahimic CGT, Chancellor J, et al. (2021) The individual and combined effects of spaceflight radiation and microgravity on biologic systems and functional outcomes. *J Environ Sci Health C Toxicol Carcinog*. 39:129-179.

57. Cheung PK, Ma MH, Tse HF, Yeung KF, Tsang HF, et al. (2019) The applications of metabolomics in the molecular diagnostics of cancer. *Expert Rev Mol Diagn*. 19:785-793.

58. Nassef MZ, Melnik D, Kopp S, Sahana J, Infanger M, et al. (2020) Breast Cancer Cells in Microgravity: New Aspects for Cancer Research. *Int J Mol Sci*. 21:7345.

59. Grimm D, Schulz H, Krüger M, Cortés-Sánchez JL, Egli M, et al. (2022) The Fight against Cancer by Microgravity: The Multicellular Spheroid as a Metastasis Model. *Int J Mol Sci.* 23:3073.

60. Dietz C, Infanger M, Romswinkel A, Strube F, Kraus A. (2019) Apoptosis Induction and Alteration of Cell Adherence in Human Lung Cancer Cells under Simulated Microgravity. *Int J Mol Sci.* 20:3601.

61. Hybel TE, Dietrichs D, Sahana J, Corydon TJ, Nassef MZ, et al. (2020) Simulated Microgravity Influences VEGF, MAPK, and PAM Signaling in Prostate Cancer Cells. *Int J Mol Sci*.21:1263.

62. Roggan MD, Kronenberg J, Wollert E, Hoffmann S, Nisar H, et al. (2023) Unraveling astrocyte behavior in the space brain: Radiation response of primary astrocytes. *Front Public Health.* 11:1063250.

63. Beumer J, Clevers H. (2021) Cell fate specification and differentiation in the adult mammalian intestine. *Nat Rev Mol Cell Biol.* 22:39-53.

64. Gehart H, Clevers H. (2019) Tales from the crypt: new insights into intestinal stem cells. *Nat Rev Gastroenterol Hepatol.* 16:19-34.

65. Kiouptsi K, Pontarollo G, Reinhardt C. (2023) Gut Microbiota and the Microvasculature. *Cold Spring Harb Perspect Med.* 13:a041179.

66. Wittwer AE, Lee SG, Ranadheera CS. (2023) Potential associations between organic dairy products, gut microbiome, and gut health: A review. *Food Res Int*. 172:113195.

67. Portincasa P, Di Ciaula A, Garruti G, Vacca M, De Angelis M, et al. (2020) Bile Acids and GPBAR-1: Dynamic Interaction Involving Genes, Environment and Gut Microbiome. *Nutrients*. 12:3709.

68. Carriot J, Mackrous I, Cullen KE. (2021) Challenges to the Vestibular System in Space: How the Brain Responds and Adapts to Microgravity. *Front Neural Circuits.* 15:760313.

69. Clément G, Wood SJ, Paloski WH, Reschke MF. (2019) Changes in gain of horizontal vestibulo-ocular reflex during spaceflight. *J Vestib Res.* 29:241-251.

70. Glukhikh DO, Naumov IA, Schoenmaekers C, Kornilova LN, Wuyts FL. (2022) The Role of Different Afferent Systems in the Modulation of the Otolith-Ocular Reflex After Long-Term Space Flights. *Front Physiol.* 13:743855.

71. Shelhamer M, Zee DS. (2003) Context-specific adaptation and its significance for neurovestibular problems of space flight. *J Vestib Res.* 13:345-62.

72. Mulavara AP, Ruttley T, Cohen HS, Peters BT, Miller C, et al. (2012) Vestibular-somatosensory convergence in head movement control during locomotion after long-duration space flight. *J Vestib Res*. 22:153-66.

73. Berardini M, Gesualdi L, Morabito C, Ferranti F, Reale A, et al. (2023) Simulated Microgravity Exposure Induces Antioxidant Barrier Deregulation and Mitochondria Enlargement in TCam-2 Cell Spheroids. *Cells.* 12:2106.

74. Lee PHU, Chung M, Ren Z, Mair DB, Kim DH. (2022) Factors mediating spaceflight-induced skeletal muscle atrophy. *Am J Physiol Cell Physiol*. 322:C567-C580.

75. Sibonga J, Matsumoto T, Jones J, Shapiro J, Lang T, et al. (2019) Resistive exercise in astronauts on prolonged spaceflights provides partial protection against spaceflight-induced bone loss. *Bone.* 128:112037.

76. Vico L, van Rietbergen B, Vilayphiou N, Linossier MT, Locrelle H, et al. (2017). Cortical and Trabecular Bone Microstructure Did Not Recover at Weight-Bearing Skeletal Sites and Progressively Deteriorated at Non-Weight-Bearing Sites During the Year Following International Space Station Missions. *Journal of bone and mineral research* : 32:2010–2021.

77. Baran R, Wehland M, Schulz H, Heer M, Infanger M, et al. (2022) Microgravity-Related Changes in Bone Density and Treatment Options: A Systematic Review. *Int J Mol Sci.* 23:8650.

78. Sibonga JD. (2013) Spaceflight-induced bone loss: is there an osteoporosis risk? *Curr Osteoporos Rep.* 11:92-8.

79. Wang E. (1999). Age-dependent atrophy and microgravity travel: what do they have in common?. FASEB journal: official publication of the *Federation of American Societies for Experimental Biolog*y, 13:S167–S174.

80. Baran R, Wehland M, Schulz H, Heer M, Infanger M, et al. (2022) Microgravity-Related Changes in Bone Density and Treatment Options: A Systematic Review. *Int. J. Mol. Sci.* 23:8650.

81. Rengel A, Tran V, Toh LS. (2023) Denosumab as a Pharmacological Countermeasure Against Osteopenia in Long Duration Spaceflight. *Aerosp Med Hum Perform*. 94:389-395.

82. Baran R, Wehland M, Schulz H, Heer M, Infanger M, et al. (2022) Microgravity-Related Changes in Bone Density and Treatment Options: A Systematic Review. *Int. J. Mol. Sci.* 23:8650.

83. Bonanni R, Cariati I, Marini M, Tarantino U, Tancredi V. (2023) Microgravity and Musculoskeletal Health: What Strategies Should Be Used for a Great Challenge? *Life* (Basel). 13:1423.

84. Iandolo D, Strigini M, Guignandon A, Vico L. (2021) Osteocytes and Weightlessness. *Curr Osteoporos Rep*. 19:626-636.

85. Tian Y, Ma X, Yang C, Su P, Yin C, et al. (2017) The Impact of Oxidative Stress on the Bone System in Response to the Space Special Environment. *Int J Mol Sci.* 18:2132.

86. Coulombe JC, Senwar B, Ferguson VL. (2020). Spaceflight-Induced

Bone Tissue Changes that Affect Bone Quality and Increase Fracture Risk. *Current osteoporosis reports,* 18:1–12.

87. Hart D A. (2023). Regulation of Bone by Mechanical Loading, Sex Hormones, and Nerves: Integration of Such Regulatory Complexity and Implications for Bone Loss during Space Flight and Post-Menopausal Osteoporosis. *Biomolecules,* 13:1136.

88. Sibonga JD, Spector ER, Keyak JH, Zwart SR, Smith SM, et al. (2020). Use of Quantitative Computed Tomography to Assess for Clinically-relevant Skeletal Effects of Prolonged Spaceflight on Astronaut Hips. Journal of clinical densitometry : the official journal of the *International Society for Clinical Densitometry*, 23:155–164.

89. kada A, Matsumoto T, Ohshima H, Isomura T, Koga T, et al. (2021) Bisphosphonate Use May Reduce the Risk of Urolithiasis in Astronauts on Long-Term Spaceflights. *JBMR Plus*. 6:e10550.

90. Smith SM, Wastney ME, O'Brien KO, Morukov BV, Larina IM, et al. (2005) Bone markers, calcium metabolism, and calcium kinetics during extended-duration space flight on the mir space station. *J Bone Miner Res.* 20:208-18.

91. Smith SM, Zwart SR, Heer M, Hudson EK, Shackelford L, et al. (2014) Men and women in space: bone loss and kidney stone risk after long-duration spaceflight. *J Bone Miner Res*. 29:1639-45.

92. Smith SM, Heer M, Shackelford LC, Sibonga JD, Spatz J, et al. (2015) Bone metabolism and renal stone risk during International Space Station missions. *Bone.* 81:712-720.

93. Penchev R, Scheuring RA, Soto AT, Miletich DM, Kerstman E, et al. (2021) Back Pain in Outer Space. *Anesthesiology*. 135:384-395.

94. Shibata S, Wakeham DJ, Thomas JD, Abdullah SM, Platts S, et al. (2023) Cardiac Effects of Long-Duration Space Flight. *J Am Coll Cardiol*. 82:674-684.

95. Davis CM, Allen AR, Bowles DE. (2021) Consequences of space radiation on the brain and cardiovascular system. *J Environ Sci Health C Toxicol Carcinog.* 39:180-218.

96. Antonutto G, di Prampero PE. (2003) Cardiovascular deconditioning in microgravity: some possible countermeasures. *Eur J Appl Physiol.* 90:283-91.

97. Beheshti A, McDonald JT, Miller J, Grabham P, Costes SV. (2019) GeneLab Database Analyses Suggest Long-Term Impact of Space Radiation on the Cardiovascular System by the Activation of FYN Through Reactive Oxygen Species. *Int J Mol Sci.* 20:661.

98. Norsk P. (2020) Adaptation of the cardiovascular system to weightlessness: Surprises, paradoxes and implications for deep space missions. *Acta Physiol (Oxf)*. 228:e13434.

99. Prisk GK, Elliott AR, West JB. (2000) Sustained microgravity reduces the human ventilatory response to hypoxia but not to hypercapnia. *J Appl Physiol* (1985). 88:1421-30.

100. Oeung B, Pham K, Olfert IM, Zerda DJ, Gaio E, et al. (2023) The normal distribution of the hypoxic ventilatory response and methodological impacts: a meta-analysis and computational investigation. *J Physiol.* 601:4423-4440.

101. Pramanik J, Kumar A, Panchal L, Prajapati B. (2023) Countermeasures for Maintaining Cardiovascular Health in Space Missions. *Curr Cardiol Rev.* 19:57-67.

102. Davis CM, Allen AR, Bowles DE. (2021) Consequences of space radiation on the brain and cardiovascular system. *J Environ Sci Health C Toxicol Carcinog*. 39:180-218.

103. Blue RS, Bayuse TM, Daniels VR, Wotring VE, Suresh R, et al. (2019) Supplying a pharmacy for NASA exploration spaceflight: challenges and current understanding. *NPJ Microgravity.* 5:14.

104. McCarthy ID. (2005). Fluid shifts due to microgravity and their effects on bone: a review of current knowledge. *Annals of biomedical engineering*, 33: 95–103.

105. Ercan E. (2021) Effects of aerospace environments on the cardiovascular system. *Anatol J Cardiol*. 25:S3-S6.

106. Aalkjær C, Wang T. (2021) The Remarkable Cardiovascular System of Giraffes. *Annu Rev Physiol*. 83:1-15.

107. Jung AS, Harrison R, Lee KH, Genut J, Nyhan D, et al. (2005) Simulated microgravity produces attenuated baroreflex-mediated pressor, chronotropic, and inotropic responses in mice. *Am J Physiol Heart Circ Physiol*. 289:H600-7.

108. Ertl AC, Diedrich A, Biaggioni I. (2000) Baroreflex dysfunction induced by microgravity: potential relevance to postflight orthostatic intolerance. *Clin Auton Res*. 10:269-77.

109. Seibert FS, Bernhard F, Stervbo U, Vairavanathan S, Bauer F, et al. (2018) The Effect of Microgravity on Central Aortic Blood Pressure. Am J Hypertens. 31:1183-1189.

110. Du J, Cui J, Yang J, Wang P, Zhang L, et al. (2021) Alterations in Cerebral Hemodynamics During Microgravity: A Literature Review. *Med Sci Monit.* 27:e928108-9.

111. Rosa E, Gronkvist M, Kolegard R, Dahlstrom N, Knez I, et al. (2021) Fatigue, Emotion, and Cognitive Performance in Simulated Long-Duration, Single-Piloted Flight Missions. *Aerosp Med Hum Perform.* 92:710-719.

112. Mammarella N, Gatti M, Ceccato I, Di Crosta A, Di Domenico A, et al. (2022) The Protective Role of Neurogenetic Components in Reducing Stress-Related Effects during Spaceflights: Evidence from the Age-Related Positive Memory Approach. *Life* (Basel). 12:1176.

113. Kanas N. (1998) Psychiatric issues affecting long duration space missions. Aviat *Space Environ Med*. 69:1211-6.

114. Dai J, Wang H, Yang L, Wen Z. (2019) Emotional Intelligence and Emotional State Effects on Simulated Flight Performance. *Aerosp Med Hum Perform*. 90:101-108.

115. Gatti M, Palumbo R, Di Domenico A, Mammarella N. (2022) Simulating Extreme Environmental Conditions via Mental Imagery: The Case of Microgravity and Weight Estimation. *Front Psycho*l. 13:913162.

116. Gupta U, Baig S, Majid A, Bell SM. (2023) The neurology of space flight; How does space flight effect the human nervous system? *Life Sci Space Res (Amst*). 36:105-115.

117. Gatti M, Palumbo R, Di Domenico A, Mammarella N. (2022) Affective health and countermeasures in long-duration space exploration. *Heliyon*. 8:e09414.

118. Wortzel JR, Norden JG, Turner BE, Haynor DR, Kent ST, et al. (2019) Ambient temperature and solar insolation are associated with decreased prevalence of SSRI-treated psychiatric disorders. *J Psychiatr Res*. 110:57-63.

119. Jardon KM, Canfora EE, Goossens GH, Blaak EE. (2022) Dietary macronutrients and the gut microbiome: a precision nutrition approach

to improve cardiometabolic health. *Gut.* 71:1214-1226.

120. Grabherr L, Mast FW. (2010) Effects of microgravity on cognition: The case of mental imagery. *J Vestib Res*. 20:53-60.

121. Marx W, Moseley G, Berk M, Jacka F. (2017) Nutritional psychiatry: the present state of the evidence. *Proc Nutr Soc.* 76:427-436.

122. Shuai M, Fu Y, Zhong HL, Gou W, Jiang Z, et al. (2022) Mapping the human gut mycobiome in middle-aged and elderly adults: multiomics insights and implications for host metabolic health. *Gut.* 71:1812-1820.

123. Ferrando AA, Paddon-Jones D, Wolfe RR. (2022) Alterations in protein metabolism during space flight and inactivity. *Nutrition.* 18:837-41.

124. Franzago M, Alessandrelli E, Notarangelo S, Stuppia L, Vitacolonna E. (2023) Chrono-Nutrition: Circadian Rhythm and Personalized Nutrition. *Int J Mol Sci*. 24:2571.

125. Perez-Pardo P, Dodiya HB, Engen PA, Forsyth CB, Huschens AM, et al. (2019) Role of TLR4 in the gut-brain axis in Parkinson's disease: a translational study from men to mice. *Gut.* 68:829-843.

126. Nerius M, Doblhammer G, Tamgüney G. (2020) GI infections are associated with an increased risk of Parkinson's disease. *Gut*. 69:1154-1156.

127. Zwart SR, Mulavara AP, Williams TJ, George K, Smith SM. (2021) The role of nutrition in space exploration: Implications for sensorimotor, cognition, behavior and the cerebral changes due to the exposure to radiation, altered gravity, and isolation/confinement hazards of spaceflight. *Neurosci Biobehav Rev*. 127:307-331.

128. Krittanawong C, Singh NK, Scheuring RA, Urquieta E, Bershad EM, et al. (2022) Human Health during Space Travel: State-of-the-Art Review. *Cells*. 12:40.

129. Albornoz-Miranda M, Parrao D, Taverne M. (2023) Sleep disruption, use of sleep-promoting medication and circadian desynchronization in spaceflight crewmembers: Evidence in low-Earth orbit and concerns for future deep-space exploration missions. *Sleep Med* X. 6:100080.

130. Petit G, Cebolla A, Fattinger S, Petieau M, Summerer L, et al. (2019) Local sleep-like events during wakefulness and their relationship to decreased alertness in astronauts on ISS. *NPJ Microgravity*.5.

131. Wu B, Wang Y, Wu X, Liu D, Xu D, et al. (2018) On-orbit sleep problems of astronauts and countermeasures. *Mil. Med. Res*. 5.

132. Gonfalone A. (2019) Hypothetical role of gravity in rapid eye movements during sleep. *Med Hypotheses*. 127:63–65.

133. Piltch O, Flynn-Evans E, Stickgold R. (2020) Changes in sleep architecture during long-duration spaceflight. *Sleep.* 43:A105–A106.

134. Whitmire A, Slack K, Locke J, Keeton K. (2013) Johnson Space Center; Houston: 2013. Sleep quality questionnaire short- duration flyers.

135. Gemignani A, Piarulli A, Menicucci D, Laurino M, Rota G, et al. (2014) How stressful are 105 days of isolation? Sleep EEG patterns and tonic cortisol in healthy volunteers simulating manned flight to Mars. *Int J Psychophysiol.* 93:211–219.

136. Tipton CM, Greenleaf JE, Jackson CG. (1996) Neuroendocrine and immune system responses with spaceflights. *Med Sci Sports Exerc.* 28:988-98.

137. Stein TP, Schluter MD, Leskiw MJ. (1999) Cortisol, insulin and leptin during space flight and bed rest. *J Gravit Physiol*. 6:P85-6.

138. Béland LC, Markovinovic A, Jakovac H, de Marchi F, Bilic E, et al. (2020) Immunity in Amyotrophic Lateral Sclerosis: Blurred Lines between Excessive Inflammation and Inefficient Immune Responses. *Brain Commun*. 2:fcaa124.

139. De Marchi F, Munitic I, Vidatic L, Papić E, Rački V, et al. (2023) Overlapping Neuroimmune Mechanisms and Therapeutic Targets in Neurodegenerative Disorders. *Biomedicines*.11:2793.

140. Hughes RL, Kable ME, Marco M, Keim NL. (2019) The Role of the Gut Microbiome in Predicting Response to Diet and the Development of Precision Nutrition Models. Part II: Results. *Adv Nutr.* 10:979-998.

141. Mhatre SD, Iyer J, Puukila S, Paul AM, Tahimic CGT, et al. (2022) Neuro-consequences of the spaceflight environment. *Neurosci Biobehav Rev*. 132:908-935.

142. Pavlović M, Jovanović I, Ugrenović S, Stojanović V, Živković V, et al. (2021) Human anterior pituitary's ACTH cells during the aging process: immunohistochemic and morphometric study. *Anat Sci Int*. 96:250-257.

143. Willey JS, Britten RA, Blaber E, Tahimic CGT, Chancellor J, et al. (2021) The individual and combined effects of spaceflight radiation and microgravity on biologic systems and functional outcomes. *J Environ Sci Health C Toxicol Carcinog.* 39:129-179.

144. Friedman E, Bui B. (2017) A Psychiatric Formulary for Long-Duration Spaceflight. *Aerosp Med Hum Perform*. 88:1024-1033.

145. Eyal S, Derendorf H. (2019) Medications in Space: In Search of a Pharmacologist's Guide to the Galaxy. *Pharm Res.* 14:148.

146. Berman E, Eyal S. (2019). Drug interactions in space: A cause for concern? *Pharmaceutical Research*, 36:114.

147. Dello Russo C, Bandiera T, Monici M, Surdo L, Yip VLM, et al. (2022) Physiological adaptations affecting drug pharmacokinetics in space: what do we really know? A critical review of the literature. *Br J Pharmacol*.179:2538-2557.

148. Houser T, Lindgren KN, Mazuchowski EL 2nd, Barratt MR, Haines DC, et al. (2023) Remains Containment Considerations for Death in Low-Earth Orbit. *Aerosp Med Hum Perform*. 94:368-376.

149. Nguyen M, Knowling M, Tran NN, Burgess A, Fisk I, et al. (2023) Space farming: Horticulture systems on spacecraft and outlook to planetary space exploration. *Plant Physiol Biochem*. 194:708-721.

150. Detsis E. (2022) Ethics in Space: The Case for Future Space Exploration.

151. Witze A. (2023) Ethics in outer space: can we make interplanetary exploration just? *Nature.* 617:245-246.

152. Sychev VN, Novikova ND, Poddubko SV, Deshevaya EA, Orlov OI. (2020) The Biological Threat: The Threat of Planetary Quarantine Failure as a Result of Outer Space Exploration by Humans. *Dokl Biol Sci*. 490:28-30.

153. Sletten TL, Sullivan JP, Arendt J, Palinkas LA, Barger LK, et al. (2022) The role of circadian phase in sleep and performance during Antarctic winter expeditions. *J Pineal Res*. 73:e12817.

154. Barger LK, Sullivan JP, Lockley SW, Czeisler CA. (2021) Exposure to Short Wavelength-Enriched White Light and Exercise Improves Alertness and Performance in Operational NASA Flight Controllers Working Overnight Shifts. *J Occup Environ Med*. 63:111-118.

155. Monk TH, Buysse DJ, Billy BD, DeGrazia JM. (2004) Using nine 2-h delays to achieve a 6-h advance disrupts sleep, alertness, and circadian rhythm. *Aviat Space Environ Med*. 75:1049-57.

156. Zivi P, De Gennaro L, Ferlazzo F. (2020) Sleep in Isolated, Confined, and Extreme (ICE): A Review on the Different Factors Affecting Human Sleep in ICE. *Front Neurosci.* 14:851.

157. Mammarella N. (2020) Towards the Affective Cognition Approach to Human Performance in Space. *Aerosp Med Hum Perform*. 91:532-534.

158. Mallis MM, DeRoshia CW. (2005) Circadian rhythms, sleep, and performance in space. *Aviat Space Environ Med*. 76:B94-107.

159. Klein T, Sanders M, Wollseiffen P, Carnahan H, Abeln V, et al. (2020) Transient cerebral blood flow responses during microgravity. *Life Sci Space Res (Amst).* 25:66-71.

160. Du J, Cui J, Yang J, Wang P, Zhang L, et al. (2021) Alterations in Cerebral Hemodynamics During Microgravity: A Literature Review. *Med Sci Monit*. 27:e928108-9.

161. Klein T, Wollseiffen P, Sanders M, Claassen J, Carnahan H, et al. (2019) The influence of microgravity on cerebral blood flow and electrocortical activity. *Exp Brain Res*. 237:1057-1062.

162. Florence G, Lemenn M, Desert S, Bourron F, Serra A, et al. (1998) Cerebral cortical blood flow in rabbits during parabolic flights (hypergravity and microgravity). *Eur J Appl Physiol Occup Physiol*. 77:469-78.

163. Committee on Ethics Principles and Guidelines for Health Standards for Long Duration and Exploration Spaceflights; Board on Health Sciences Policy; Institute of Medicine. (2014) *Health Standards for Long Duration and Exploration Spaceflight: Ethics Principles, Responsibilities, and Decision Framework*. Kahn J, Liverman CT, McCoy MA, editors. Washington (DC): National Academies Press (US).

164. Rienecker KDA, Paladini MS, Grue K, Krukowski K, Rosi S. (2021). Microglia: Ally and Enemy in Deep Space. *Neuroscience and biobehavioral reviews,* 126:509–514.

165. Klein T, Sanders M, Wollseiffen P, Carnahan H, Abeln V, et al. (2020) Transient cerebral blood flow responses during microgravity. *Life Sci Space Res* (Amst). 25:66-71.

166. Nau R, Blei C, Eiffert H. (2020) Intrathecal Antibacterial and Antifungal Therapies. *Clin Microbiol Rev*. 33:e00190-19.

167. Ichijo T, Shimazu T, Nasu M. Microbial (2020) Monitoring in the International Space Station and Its Application on Earth. *Biol Pharm Bull.* 43:254-257.

168. Nielsen S, White K, Preiss K, Peart D, Gianoulias K, et al. (2021) Growth and Antifungal Resistance of the Pathogenic Yeast, Candida Albicans, in the Microgravity Environment of the International Space Station: An Aggregate of Multiple Flight Experiences. *Life (Basel).* 11:283.

169. Kass EH. (1971) Resistance to infections in extended space flight. *Life Sci Space* Res. 9:35-41.

170. Pavletić B, Runzheimer K, Siems K, Koch S, Cortesão M, et al. (2022) Spaceflight Virology: What Do We Know about Viral Threats in the Spaceflight Environment? *Astrobiology.* 22:210-224.

171. Ichijo T, Uchii K, Sekimoto K, Minakami T, Sugita T, et al. (2022) Bacterial bioburden and community structure of potable water used in the International Space Station. *Sci Rep.* 12:16282.

172. Landry KS, Morey JM, Bharat B, Haney NM, Panesar SS. (2020) Biofilms-Impacts on Human Health and Its Relevance to Space Travel. *Microorganisms.* 8:998.

173. Netea MG, Domínguez-Andrés J, Eleveld M, Op den Camp HJM, van der Meer JWM, et al. (2020) Immune recognition of putative alien microbial structures: Host-pathogen interactions in the age of space travel. *PLoS Pathog*. 16:e1008153.

174. Hicks J, Olson M, Mitchell C, Juran CM, Paul AM. (2023) The Impact of Microgravity on Immunological States. *Immunohorizons*. 7:670-682.

175. Gallardo-Dodd CJ, Oertlin C, Record J, Galvani RG, Sommerauer C, et al. (2023) Exposure of volunteers to microgravity by dry immersion bed over 21 days results in gene expression changes and adaptation of T cells. *Sci Adv*. 9:eadg1610.

176. Akiyama T, Horie K, Hinoi E, Hiraiwa M, Kato A, et al. (2020) How does spaceflight affect the acquired immune system? *NPJ Microgravity.* 6:14.

177. Horie K, Kato T, Kudo T, Sasanuma H, Miyauchi M, et al. (2019) Impact of spaceflight on the murine thymus and mitigation by exposure to artificial gravity during spaceflight. *Sci. Rep*. 9:19866.

178. Mehta SK, Laudenslager ML, Stowe RP, Crucian BE, Sams CF, et al. (2014) Multiple latent viruses reactivate in astronauts during Space Shuttle missions. *Brain Behav Immun.* 210-7.

179. Jacob P, Oertlin C, Baselet B, Westerberg LS, Frippiat JP, et al. (2023) Next generation of astronauts or ESA astronaut 2.0 concept and spotlight on immunity. *NPJ Microgravity* 9:51.

180. Corydon TJ, Schulz H, Richter P, Strauch SM, Böhmer M, et al. (2023) Current Knowledge about the Impact of Microgravity on Gene Regulation. *Cells.* 12:1043.

181. Krittanawong C, Singh NK, Scheuring RA, Urquieta E, Bershad EM, et al. (2022) Human Health during Space Travel: State-of-the-Art Review. *Cells.* 12:40.

182. Roads BD, Love BC. Modeling Similarity and Psychological Space. Annu Rev Psychol. 2023 Aug 10. doi: 10.1146/annurev-psych-040323-115131. Epub ahead of print. PMID: 37562499.

183. Prasad B, Grimm D, Strauch SM, Erzinger GS, Corydon TJ, et al. (2020) Influence of Microgravity on Apoptosis in Cells, Tissues, and Other Systems In Vivo and In Vitro. *Int J Mol Sci*. 21:9373.

184. Drago-Ferrante R, Di Fiore R, Karouia F, Subbannayya Y, Das S, et al. (2022) Extraterrestrial Gynecology: Could Spaceflight Increase the Risk of Developing Cancer in Female Astronauts? An Updated Review. *Int J Mol Sci*. 23:7465.

185. Corydon TJ, Schulz H, Richter P, Strauch SM, Böhmer M, et al. (2023) Current Knowledge about the Impact of Microgravity on Gene Regulation. *Cells.* 12:1043.

186. Kamal KY, Lawler JM. (2023) Cellular and Molecular Signaling Meet the Space Environment. *Int J Mol Sci.* 24:5955.

187. Rea G, Cristofaro F, Pani G, Pascucci B, Ghuge SA, et al. (2016). Microgravity-driven remodeling of the proteome reveals insights into molecular mechanisms and signal networks involved in response to the space flight environment. *Journal of proteomics*, 137:3–18.

188. Kamal KY, Lawler JM. (2023) Cellular and Molecular Signaling Meet the Space Environment. *Int J Mol Sci*. 24:5955.

189. Tobin BW, Uchakin PN, Leeper-Woodford SK. (2002) Insulin secretion and sensitivity in space flight: diabetogenic effects. *Nutrition.* 18:842-8.

190. Crucian BE, Choukèr A, Simpson RJ, Mehta S, Marshall G, et al. (2018) Immune system dysregulation during spaceflight: Potential

countermeasures for deep space exploration missions. *Front. Immunol.* 9:1437.

191. Lv H, Yang H, Jiang C, Shi J, Chen RA, et al. (2023) Microgravity and immune cells. *J R Soc Interface.* 20:20220869.

192. Sun Y, Kuang Y, Zuo Z. (2021) The Emerging Role of Macrophages in Immune System Dysfunction under Real and Simulated Microgravity Conditions. *Int J Mol Sci*. 22:2333.

193. Ponomarev SA, Sadova AA, Rykova MP, Orlova KD, Vlasova DD, et al. (2022) The impact of short-term confinement on human innate immunity. *Sci Rep.* 12:8372.

194. Capri M, Conte M, Ciurca E, Pirazzini C, Garagnani P, et al. (2023) Long-term human spaceflight and inflammaging: Does it promote aging? *Ageing Res Rev.* 87:101909.

195. Simon Á, Smarandache A, Iancu V, Pascu ML. (2021) Stability of Antimicrobial Drug Molecules in Different Gravitational and Radiation Conditions in View of Applications during Outer Space Missions. *Molecules.* 26:2221.

196. Dhar S, Kaeley DK, Kanan MJ, Yildirim-Ayan E. (2021) Mechano-Immunomodulation in Space: Mechanisms Involving Microgravity-Induced Changes in T Cells. *Life (Basel).* 11:1043.

197. Yan L, Sun C, Zhang Y, Zhang P, Chen Y, et al. (2023) The Biological Implication of Semicarbazide-Sensitive Amine Oxidase (SSAO) Upregulation in Rat Systemic Inflammatory Response under Simulated Aerospace Environment. *Int J Mol Sci.* 24:3666.

198. Zhao S, Pei S, Wang A, Chen Y, Zhang P, et al. (2021) Possible role of a dual regulator of neuroinflammation and autophagy in a simulated space environment. *Acta Astronaut*. 187:181–189.

199. Rcheulishvili N, Papukashvili D, Deng Z, Wang S, Deng Y. (2021) Simulated microgravity alters the expression of plasma SSAO and its enzymatic activity in healthy rats and increases the mortality in high-fat diet/streptozotocin-induced diabetes. *Life Sci. Space Res*. 30:24–28.

200. Kim M, Jang G, Kim KS, Shin J. (2022) Detrimental effects of simulated microgravity on mast cell homeostasis and function. *Front Immunol*.13:1055531.

201. ElGindi M, Sapudom J, Ibrahim IH, Al-Sayegh M, Chen W, et al. (2021) May the Force Be with You (Or Not): The Immune System under Microgravity. *Cells.* 10:1941.

202. Dhar S, Kaeley DK, Kanan MJ, Yildirim-Ayan E. (2021) Mechano-Immunomodulation in Space: Mechanisms Involving Microgravity-Induced Changes in T Cells. *Life* (Basel). 11:1043.

203. Bevelacqua JJ, Mortazavi SA, Welsh JS, Mortazavi SMJ. (2023) How Reactivation of SARS-CoV-2 in Astronauts with Dysregulated Immune Systems Can Negatively Affect the Odds of Success in Future Space Missions. *J Biomed Phys Eng.* 13:297-298.

204. Nicholson WL, Munakata N, Horneck G, Melosh HJ, Setlow P. (2000) Resistance of Bacillus endospores to extreme terrestrial and extraterrestrial environments. *Microbiol Mol Biol Rev.* 64:548-72.

205. Ilyin V, Orlov O, Skedina M, Korosteleva A, Molodtsova D, et al. (2023) Mathematical Model of Antibiotic Resistance Determinants' Stability Under Space Flight Conditions. *Astrobiology.* 23:407-414.

206. Dello Russo C, Bandiera T, Monici M, Surdo L, Yip VLM, et al. (2022) Physiological adaptations affecting drug pharmacokinetics in space: what do we really know? A critical review of the literature. *Br J Pharmacol.*179:2538-2557.

207. Higginson EE, Galen JE, Levine MM, Tennant SM. (2016) Microgravity as a biological tool to examine host-pathogen interactions and to guide development of therapeutics and preventatives that target pathogenic bacteria. *Pathog Dis.* 74:ftw095.

208. Lombini M, Schreiber L, Albertini R, Alessi EM, Attinà P, et al. (2023) Solar ultraviolet light collector for germicidal irradiation on the moon. *Sci Rep.* 13:8326.