# Human Health in Space Travel: Limitations and Opportunities

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# Abstract

Space travel presents unique environmental challenges that enact molecular, cellular, and physiological changes across many regions within the human body. Specifically, the high energy and variable mass of the particles from space radiation present new and unexplored consequences in which astronauts will be at greater risk of deleterious health effects beyond Earth's protective magnetosphere. Longer missions beyond low Earth orbit will result in greater doses of space radiation, increasing the risk of developing degenerative tissue diseases from the accumulation of genetic mutations and high oxidative stress. This thesis maps the findings of space-related biological research on humans and animals exposed to spaceflight effects –to present the risks associated with spaceflight, health responses to these risks, and the mitigative strategies that can be applied to counteract deleterious health effects and ensure successful spaceflight missions in the future.

Key terms: spaceflight, aerospace medicine, space biology, oxidative stress, DNA damage, galactic cosmic ray

# Introduction

"Man must rise above Earth to the top of the atmosphere and beyond, for only then will he fully understand the world in which he lives" – Socrates (469-399 BC). Human fascination with space travel transcends thousands of years to the present. This thesis sheds light upon this age-old-persisting-into-modern-age fascination regarding if humans could survive in outer space and inquires what steps should be taken towards interplanetary travel.

This paper begins with an overview of space radiation, acknowledging that multiple environmental factors of space occur in conjunction with one another. Focusing on space radiation, this paper next presents known and hypothetical health problems to which current research is focused on detecting and developing countermeasures to address. Integrative strategies to preserve the health and well-being of future astronauts are then elaborated upon. Finally, the pressing limitations of current studies are discussed where the preliminary state of space health research limits the understanding of the long-term human health effects of the spaceflight environment because of complex responses. Spaceflight conditions are still new to human experience and present many uncertainties when attempting to delineate concrete causal relationships between specific environmental factors of space with observed changes in health.

Overall, this thesis communicates the pressing need for more space radiation health studies in the deep space environment and concludes by outlining future research needed for the development of ethical solutions to the problems astronauts face.

# Background

Aerospace medicine studies the unique physiological responses human bodies have within the environment of space. One obstacle this field confronts is the health changes associated with exposure to space radiation. Space radiation is categorized into Galactic Cosmic Rays (GCR) and Solar Particle Events (SPE), as well as secondary particles resulting from the collisions between space radiation and spacecraft shielding materials in a process known as spallation (Chancellor et al., 2014). Many studies on this topic have been conducted aboard the International Space Station (ISS), where Earth's magnetosphere shields most of the high energy and high charge (HZE) particles (Hassler et al., 2014). However, there is a lack of research that successfully models these complex factors to which astronauts are constantly exposed. The limited current knowledge regarding the risks and hazards that endanger human health in the space environment needs to be addressed in the advent of longer-duration missions beyond low Earth orbit and outside of Earth's magnetosphere.

NASA is shifting its focus from 6-month low orbit missions to future lunar missions and Mars flights that can be expected to last 3-4 years (Heilweil et al., 2022). This dramatic change in distance and duration demands astronauts be able to operate safely under extreme conditions. The reality of deep space travel is further acknowledged by the White House with its "National Cislunar Science and Technology Strategy" announcement in plans to bring humans back to the moon by 2025 (Heilweil et al., 2022). This announcement came after the recent success of launching Artemis 1 - the farthest lunar flyby mission for a vehicle designed for human astronauts (Heilweil et al., 2022). Scientists will need to consider the health risks of missions beyond the low Earth orbit as astronauts will be faced with increased doses and longer exposure to galactic cosmic rays (GCRs) and high-intensity solar particle events (SPEs). This thesis

reviews the hazards of spaceflight including the psychological and physical health of astronauts, the limitations of spaceflight biological research, and the potential mitigative strategies under development.

## Galactic Cosmic Rays (GCR)

Radiation is a major spaceflight hazard that damages DNA, RNA, proteins, and lipids and causes oxidative stress in cells (Goodwin & Christofidou-Solomidou, 2018). Space radiation dose varies with the distance from Earth: ISS astronauts are exposed to 100–200 milliSievert (mSv) per year and are expected to be exposed to approximately 350 mSv/year in future Mars missions. These values should be interpreted considering the annual exposure limit of 50 mSv/year on Earth (Cucinotta, 2010). The first source of space radiation is GCRs, which originate from galactic events beyond our solar system and are composed of a wide range of particles including electrons, positrons, protons, and heavy ions (Norbury et al., 2016). GCR particles move at nearly the speed of light and are theorized to be the accelerated remains of supernovae from within the Milky Way (Niemantsverdriet et al., 2012). Long-term exposure to GCR is the most concerning for human health because it cannot be shielded by the materials currently employed to construct the hulls of spacecraft (Ferrone et al., 2021). The energies of GCR ions, especially those of heavier mass, collide with the hull material and produce smaller sub-particles of lighter mass and lower energy that can cascade into astronauts through spallation (Gadioli et al., 1998). Spallation results in sub-particles of greater potential for biological damage than the original particle. The high penetration and high energy deposition of these particles make them a significant contributor to tissue damage (Niemantsverdriet et al., 2012).

## Solar Particle Events (SPE)

The second source of space radiation is SPEs, which originate from solar flares and coronal mass ejections on the sun. SPEs release enormous bursts of ionizing radiation that are hard to predict in advance and are notably more hazardous to astronauts outside of a shielded spacecraft (Cengel et al., 2010). These events release massive amounts of energy through gamma rays and protons with broad energy distributions from 10 MeV to several GeV in magnitude (Smart & Shea, 2003). SPEs are further divided into two groups based on how they are accelerated and emitted from the sun: gradual events are caused by shocks in the upper corona and lead to coronal mass ejections (CME) of the highest particle intensities, while impulsive events are caused by highly randomized solar flares and produce short-duration and low-intensity particle waves. Of the two, CMEs are the most dangerous to humans outside of Earth's protective atmosphere. While most SPEs can be eliminated due to their lower energy and lower atomic weight distributions than GCRs, occasional high fluence events such as the large SPE in October 1989 delivered doses as high as 1454 mSv/hour with 10-15% of the total fluence to have consisted of protons energized above 100 MeV (Kim et al., 2009). Astronauts exposed to such an event would be at acute risk of radiation poisoning in addition to many long-term risks after the mission (Kim et al., 2009).

## Energy Transfer of Space Radiation

Radiation is further classified as 1) ionizing or non-ionizing and 2) direct or indirect transfer of energy (Lorenz & Congdon, 1954). Charged particle radiation is often ionizing which

has the energy capabilities of “ionizing” its surroundings by removing electrons from the molecules it transits (Lorenz & Congdon, 1954). Non-charged particles including photons exert non-ionizing radiation that are unable to ionize particles and are absorbed or blocked by spacecraft hull material (Clowdsley et al., 2005). In comparison, ionizing radiation is tougher to mitigate as it penetrates the spacecraft and exposes astronauts to radiation-associated hazards (Clowdsley et al., 2005). Hazards including damage to DNA could mean cancer later in life or even acute radiation poisoning during the mission (Tang et al., 2015). Charged particle radiation further differs from non-charged particles through its direct ionization mechanism of energy transfer where health effects result from direct interactions between the tissue and particle. Charged particles successively lose energy through the tissue and damage the tissue with each energy loss, as opposed to non-charged particles' indirect ionization which generates the release of charged particles that eventually causes tissue damage (Dertinger et al., 1970). Altogether, the particle’s charge, mass, and energy arbitrate the distance it penetrates and the energy it releases in the matter the particle interacts with. For biological tissues, the dose of radiation absorbed by a particular organ is defined by these factors. The energy deposited over the travel distance of the particle is measured by linear energy transfer (LET) (Cucinotta, 2006). Overall, the space radiation of greatest concern to astronaut safety is GCRs of ionizing and high LET capabilities occurring at low, chronic doses (Cucinotta, 2010; Zeitlin et al., 2013).

## Biological Responses to Radiation

Changes in response to radiation are known to cause varying physiological effects on astronauts (Garrett-Bakelman et al., 2019). The main concerns are vascular changes (Garrett-Bakelman et al., 2019), genetic mutations (Garrett-Bakelman et al., 2019), immune dysfunction

(Pariset et al., 2020), and even cancer (Tang et al., 2015). The fundamental principles of these disorders are thought to be from the accumulation of DNA damage and oxidative stress within cells. Neurological studies have also suggested a relationship between central nervous system (CNS) impairments and chronic radiation exposure, supported by epidemiological studies (Clément et al., 2020). Thus, astronaut career limits are established on lifetime cancer mortality risks at 3%, limiting the duration and distance of current spaceflights (Cucinotta et al., 2010). Despite precautions put in place, astronauts are exposed to higher levels of ionizing radiation than professional radiation workers on Earth. Radiation exposure is also most likely to occur at very low doses (less than 1 mSv) over long periods, making it necessary to study human health in response to chronic, low-dose ionizing radiation (Zeitlin et al., 2013).

## DNA Damage

DNA is damaged by ionizing radiation through either single-strand breaks or double-strand breaks (DSB); importantly, repairing these breaks involves complex mechanisms with the possibility of error (Tang et al., 2015). The accumulation of double-strand breaks leads to mutation and eventual cancer formation (Tang et al., 2015). Unlike non-ionizing radiation, high energy high charge (HZE) particles penetrate deeper into the body and leave distinct regions of irradiated tissue. The DSBs in these regions of the tissue cluster into focal points that repair significantly slower than individual DSBs characterized by normal aging (Pariset et al., 2020). In addition to environmental effects, DSBs are further propagated by genetic predisposition. Astronauts with dysfunctional tumor-suppressor genes and when exposed to higher amounts of ionizing radiation are at an even greater risk of cancer (Pariset et al., 2020). DNA damage in astronauts was most recently studied by Garrett-Bakelman et al. (2019), where NASA conducted

a twin study to monitor the changes in human health when in spaceflight. Keeping one twin on Earth as control, the other genetically identical astronaut twin was monitored throughout a one-year mission aboard the ISS. Garrett-Bakelman et al. (2019) observed increased DNA damage through chromosomal inversions, which persisted over 6 months post-mission. Radiation-induced biomolecular damage was observed by Cucinotta et al. (2008), where multi-color fluorescence *in situ* hybridization was used to depict chromosomal shifts in the lymphocytes of astronauts. Both Cucinotta et al. (2008) and Garrett-Bakelman et al. (2019) observed significant changes to chromosomal DNA in astronauts with discernable physiological effects on human cells. However, the understanding of the mechanisms behind the aforementioned observations in association with space radiation is still inconclusive. There thus exists a great need for further analysis of how space radiation-based DNA damage occurs in comparison to terrestrial radiation models.

One area of great interest to NASA is the advancement of disease prediction models that factor in the genetic predisposition of individuals. Genetic models can potentially select for astronaut candidates more resilient to spaceflight-associated disorders, cater medications according to genetic differences, and locate genome regions that are more susceptible to space radiation damage. Computational machine learning models can then integrate the identified regions of instability to quantify the risks of radiation-induced diseases (Chancellor et al., 2014). Furthermore, single-cell RNA sequencing of the identified unstable loci enables the analysis of the cellular environment through protein expression data of isolated cell types (Huang et al., 2018). Multivariable approaches combining cell sequencing techniques with machine learning algorithms could be critical in the ongoing effort to understand and predict the disease phenotype and progression of space radiation-induced DNA damage.

## Oxidative Stress

Oxidative stress is the dysfunction in the production and accumulation of free radical Oxygen and/or Nitrogen species in cells and tissues, damaging the DNA, enzymes, and cell/tissue structure. Free radicals are molecular species containing an unpaired electron, which leads to unstable and highly reactive species capable of damaging their surroundings through oxidation or reduction (Cheeseman et al., 1993). Reactive species are normally well-regulated within the mitochondria and are used extensively in cellular respiration. However, these highly reactive species can persist in all parts of the cell. When dysregulated, free radicals damage macromolecules such as protein, DNA, carbohydrates, and lipids important to biological function (Lobo et al., 2010).

Goodwin & Christofidou-Solomidou (2018) asserts that chronic exposure to space radiation is the cause of higher levels of reactive oxygen (ROS) in astronauts aboard the ISS. The higher levels of ROS are believed to be caused by dysfunction in the mitochondria, as shown by the reduced expression of mitochondrial oxidative phosphorylation genes in astronauts (Garrett-Bakelman et al., 2019). In addition to genetic changes, free radicals are produced within the mitochondria through ionizing radiation (Leach et al., 2001). Important oxidative phosphorylation protein structures such as complexes I, II, and III are hypersensitive to oxidation. ROS damage to the iron-sulfur centers of these complexes leads to decreased metabolism and destabilized free radical regulation in the cell. Furthermore, mitochondrial DNA lacks the protective histone structures and complicated DNA repair mechanisms present in nuclear DNA, making mitochondrial structures more vulnerable to DNA damage (Wiseman et

al., 1996). These changes all have compounding effects on the molecular environment of the mitochondria and can all be attributed to astronaut health risks.

## Health Disorders in Astronauts

The cellular and tissue responses outlined in the Biological Responses to Radiation section underlie many of the physiological risks astronauts face in space. These health risks variably occur across the entire human body and manifest differently depending on which organ system is affected. This section reviews the disorders governing astronaut performance and health - including the visual center, the central nervous system, and the organ systems reportedly most at risk of cancer – associated with long-term GCR exposure.

### Space-Associated Neuro-ocular Syndrome (SANS)

According to Lee et al. (2020), SANS is the grouping of symptoms faced exclusively by astronauts during long-duration flights. Primarily affecting the eye and brain, this syndrome is new to the field of aerospace medicine and the definition of the disorder has been repeatedly refined over the past decade (Lee et al., 2020). Although a formal designation of the disorder has not been certified, SANS encompasses optic disc edema, globe flattening, folding of the choroids and retina, and hyperopic refractive shifts (> 0.75 diopters) resulting in blurry vision (Lee et al., 2020). The exact mechanism behind how the disorder develops is not fully understood, but recent studies from da Silveira et al. (2020) suggest it is an amalgamation of mitochondrial dysfunction, oxidative stress, and heightened intracranial pressure (ICP) due to fluid shifts within the brain. The microgravity environment is believed to cause blood and cerebrospinal fluid to

build up beyond the physiological level, causing swelling of several nerves and the redistribution of blood veins behind the eye (da Silveira et al., 2020). Other factors that have been linked to increased ICP include “high salt diets, rigorous resistive exercise, exposure to elevated ambient CO2 levels, and possible defects in the vitamin B12-dependent 1-carbon transfer pathways” (Zwart et al., 2012). In addition, these factors all contribute to a higher risk of endothelial dysfunction caused by edema and weakened vessel structure in astronauts. All these factors support the notion that SANS, much like many other space health changes, is multifactorial and requires further studies to understand the degree to which genomic and environmental variables contribute to its development.

## Cataracts

Among a multitude of unique experiences, astronauts report witnessing strange flashes of light in the back of their eyes. These flashes of space radiation pierce through current spacecraft shielding and are linked to the recorded effect of early onset cataracts commonly found in astronauts. Cucinotta et al., (2001) first observed this trend in 39 former astronauts who suffered some form of cataracts 5-10 years post-mission. 36 of those 39 had flown high radiation exposure missions such as the Apollo moon landing (Cucinotta et al., 2001). The 5-year longitudinal NASA Study of Cataracts in Astronauts (NASCA) reported significantly higher variability and median occurrence of cataracts in post-mission astronauts in comparison to subjects of similar ages (Chylack. et al., 2009). Cataracts are the clouding of the epithelial lens of the eye and are common to the aging process (Chylack. et al., 2009). Early cataracts in astronauts may be associated with early-onset aging symptoms via exposure to long-term space radiation.

The post-mission prevalence of cataracts calls for further inquiry into GCR interaction with the epithelial lens tissue and the continued longitudinal study of cataract formation in retired astronauts. In an ongoing unpublished study led by Eleanor Blakely at the Lawrence Berkeley National Laboratory, the mechanism behind radiation-induced cataracts is studied by exposing human eye tissue to GCR components (Blakely et al., 2021). Through genomic sequencing, the team found that Fibroblast Growth Factor 2 (FGF-2) was upregulated over eight-fold in irradiated eye tissue (Blakely et al., 2021). This gene has cascading effects in activating p21 and p53, leading to an imbalance in the control of epithelial-fiber lens cell metaplasia (Blakely et al., 2021). The mutation of p21 and p53 is suspected to decrease functional fiber lens cell formation and damage existing fiber lens cells (Blakely et al., 2021). Dead fiber lens cells begin to clump within the epithelial lens leading to a gradual clouding of vision and then ultimately manifesting as cataracts in astronauts (Blakely et al., 2021). The accumulation of dead fiber cells can take years after missions before being visibly noticeable, which delays research and complicates efforts to pinpoint the cause of the damage (Blakely, 2003). The emergence of early detection of cataracts is invaluable due to the long asymptomatic period astronaut patients wait. Methods such as dynamic light scattering probes have been developed to detect cataracts years in advance (Zambrano et al., 2012). The monitoring of FGF-2 crosstalk with other genes of interest can also potentially elucidate the mechanism behind spaceflight-induced cataracts (Blakely, 2003). A deeper understanding of cataract susceptibility in space travel enables the development of preventative measures to ensure the well-being of astronauts during and after missions.

## Radiation-Induced Carcinogenesis

The risk of cancer due to space radiation has been a primary concern since the beginning of humanity's efforts to reach space (Cucinotta, 2006). Cancer risk has been extensively studied through longitudinal models, showing higher induction of certain tumors, and giving rise to cancer risk predictions based on computational modeling (Low et al., 2019).

In mouse models, radiation-induced cancer incidence has been simulated with GCR components reproduced on Earth. HZE particle exposure data shows a higher incidence of hepatocellular carcinoma (Weil et al., 2014), mammary tumors (Illa-Bochaca et al., 2014), colorectal cancer (Datta et al., 2013), and skin cancer (Burns et al., 2007). There also exists a concern pertaining to novel disease types in the spaceflight environment. However, HZE particle exposure did not introduce new/previously undiscovered cancer types in mouse subjects (Bielefeldt-Ohmann et al., 2012).

Retrospective astronaut studies have also been conducted to analyze the cancer risk and mortality rates of spending long periods aboard the ISS. The data analyzed by Reynolds et al. (2019) indicates that past astronauts have not been statistically significantly more susceptible to cancer mortality in comparison to the general population. Reynold's (2019) study concludes that in low-orbit missions, space radiation is not shown to play as significant of a role in disease mortality. This contradiction to radiation-disease concerns does not disprove the danger of space travel but instead suggests that the mechanism behind carcinogenesis in persistent low levels of high LET in space may be different from the current understanding of acute low LET radiation. The lack of knowledge about exposure to space radiation is further established in astronaut career exposure limits, where NASA sets strict dose limits based on historical data modeling projected cancer risks. However, current risk analysis measurements are inaccurate as they are scaled from low LET radiation data, which is different from what astronauts are exposed to in

space (Cucinotta, 2006). Furthermore, there is no human data for evaluating cancer risk from GCR components. According to Cucinotta (2006), current risk models are derived from the data of acute low LET atomic bomb survivors which have different compositions and energy deposition patterns from high LET HZE particles in GCR radiation.

Computational modeling is utilized to predict cancer risk in humans and will be invaluable in efforts to model the risk posed by space radiation. Furthermore, the advent of tissue modeling and the maturation of systems biology potentiate further opportunities to analyze human data in realistic space travel circumstances (Low et al., 2019). Pariset et al. (2020) recently attempted to map human data through tissue models in a study of 674 healthy lymphocyte donors in response to GCR components. Although this study is unpublished, the data can be used to train future machine-learning models to predict actual human responses to GCR radiation. Tissue modeling provides a sanguine outlook for the direction of future ethical research that can be done to collect human response data. Overall, radiation-induced cancer is a primary concern for deep-space exploration and its complexity requires additional data to fully understand how different components and dose fractionation function in the carcinogenesis of different cancer types.

## Neurodegenerative Risk of the Central Nervous System

Neurodegenerative risk is a primary health concern of spaceflight. Current radiation data are extensively based on animal studies, specifically mouse models (Bishawi et al., 2022). Simulations point to cognitive and behavioral defects which resemble aging and neurodegenerative disorders related to oxidative stress, enteropathy, and tissue inflammation

(Clément et al., 2020). However, many of these effects are dose-dependent and do not scale linearly with exposure. Spatial learning and active memory recall have been the most extensively studied in mice, where acute and long-term impairments in "hippocampus-dependent memory formation, frontal cortex-dependent executive function and cognition, and amygdala-dependent anxiety and fear" are quantitatively recorded through electroencephalography (Clément et al., 2020). It is hypothesized that prolonged radiation damage to the brain could worsen pre-existing aging disorders, in addition to the risk of introducing new damage to the CNS.

Neurodegenerative symptoms also correspond to the physiological damage observed in irradiated mouse brains. Mice exposed to particle doses comparable to that in a Mars mission were found to have impaired hippocampus-based memory and recognition (Krukowski et al., 2018). Damage to neurons and cognitive decline persisted beyond the initial radiation event, suggesting permanent damage to the brain structure due to space radiation. Parihar et al. (2018) continually exposed mice to low levels of helium ions to replicate GCR radiation in space and found permanent changes to the circuitry between the hippocampus and the perirhinal cortex (PRC) – responsible for recognition and memory. Furthermore, these changes coincide with elevated neuroinflammation in the same afflicted brain region, revealing that "even sparsely ionizing particles" can permanently disrupt neural function and structure (Parihar et al., 2018). This extreme sensitivity could be attributed to the killing of precursor neuron cells by the changes in microglia activity during heightened neuroinflammation.

In retrospective longitudinal astronaut studies, changes to brain plasticity and shifts in gray matter distribution coincided with performative declines (Garrett-Bakelman et al. 2019; Koppelmans et al. 2016). Koppelmans et al. (2016) took MRI scans of the brains of 27 astronauts and found gray matter loss in the temporal poles, frontal poles, and orbits compared to age-

matched controls. These tissue changes concur with the spaceflight changes in cognition noted by Garrett-Bakelman et al. (2019) and are notably greater in the ISS crew in comparison to the space shuttle crew. These observations support the theory that longer exposure to space radiation could have complex compounding effects on astronauts, as supported by the conclusions posed by mouse studies (Clément et al., 2020).

## Detection for Spaceflight Biomarkers

The monitoring of astronauts within the space environment can be utilized to inform simulations on Earth and lead to the development of mitigative strategies focused on risk identification and prediction. Circulating molecules including nucleic acids and proteins are some of the many biological targets studied as indicators of spaceflight-induced health changes (Brojakowska et al., 2022; Malkani et al., 2020). MicroRNAs and clonal hematopoiesis (CH) genetic markers are regulatory factors present in the blood and have important roles in disease progression (Brojakowska et al., 2022; Malkani et al., 2020). These molecules serve as potential biomarkers for astronaut health changes and in the development of countermeasures to space radiation health risks. Furthermore, countermeasures including personalized therapies and magnetic shielding in spaceship design are also discussed in this section. These strategies supersede risk identification and must be further examined for the safety of future astronauts.

### MicroRNAs in Response to Radiation

MicroRNAs (miRNA) are small non-coding nucleic acids (> 22 nucleotides) that are central in the regulation of gene expression by binding to and silencing post-transcribed messenger RNAs (Gebert & MacRae, 2019). miRNAs are highly conserved across every

organism and can exist in all bodily fluids - including blood (Da Silva et al., 2015). 90% of miRNA is persistent enough to be found circulating in the blood and other fluids (Da Silva et al., 2015). Furthermore, miRNA is increasingly shown to play a substantial regulatory role associated with biological responses to radiation (Malkani et al. 2020). Malkani et al. (2020) reported circulating miRNA signatures are linked to multiple pathways involved with cell and tissue repair in the spaceflight environment. Comparing the miRNA expression signatures of the NASA twins study with mouse signature responses to spaceflight, Malkani et al. (2020) demonstrated its connection to the mammalian target of rapamycin (mTOR) and growth factor-beta 1 (TGFβ1) which regulate ROS/RNS oxidative stress and oxidative phosphorylation processes (Abe et al., 2013; Garrett-Bakelman et al., 2019; Malkani et al., 2020). miRNA signatures are also correlated to abnormal fatty-acid metabolism and biosynthesis which itself is linked to DNA damage and ROS dysfunction (Abe et al., 2013). DNA damage associated with miRNA signatures is further supported by clinical cancer research studies which have reported miRNA-induced chromosome instability and telomere fragility in response to space radiation (Dinami et al., 2014). Overall, miRNAs can be utilized to monitor biological responses to spaceflight and to serve as a potential biomarker in the development of countermeasures to acute and long-term health risks.

## Clonal Hematopoiesis and the Accumulation of Mutations

The accumulation of mutations in tissues and cells grows over time in the natural aging process due to inherent faults in DNA replication events (Blokzijl et al., 2016). As humans age, tissues become more diversified with differently mutated cells. These varying cell populations undergo somatic mosaicism within their original tissues and propagate according to selective

pressures (Alexandrov et al., 2015). In a process known as clonal hematopoiesis (CH), aged blood cell populations with oncogenic mutations propagate at higher rates than those without and overtake healthy blood cell populations (Jaiswal et al., 2014). Linked to adverse outcomes including hematologic cancers and cancer mortality, CH is an age-related disorder. However, in a 2020 retroactive study of former astronaut blood samples, Mencia-Trinchant et al. (2020) detected somatic mutations in astronauts twenty years earlier than the average age at which the disorder is typically found. These observations suggest the spaceflight environment could accelerate symptoms of aging in blood-forming cells. The detection of somatic mutations is thus potentially invaluable in further understanding the biological effects of radiation and in monitoring the health of astronauts.

## Countermeasures to Spaceflight Health Effects

To ensure the success of future space missions, astronauts are expected to maintain high performance over long periods and under extreme conditions. Clément et al. (2020) argue that astronauts returning to Earth from 6-month ISS missions already exhibit changes in locomotion such as muscle fatigue, ataxia, and the slowing of major reflexes. Spaceflights to the Moon and Mars will occur over longer distances and longer durations, exposing astronauts to greater and longer doses of space radiation. Physiological changes from spaceflight could impair functions in all parts of the body, making it necessary to consider strategies from multiple fields of study.

### Active Magnetic Spacecraft Shielding

Spacecraft shielding is the first line of defense working to either absorb and slow down the energy of HZE particles or to deflect and alter the trajectory away from the spacecraft altogether (Ferrone et al., 2023). The challenge of shielding is finding an alternative that can block a wide spectrum of radiation while being feasibly implemented aboard a spacecraft. Currently, hydrogen-rich polyethylene is used as passive shielding aboard the ISS which has been sufficient in reducing radiation exposure below NASA's lifetime exposure limits on 6-month low orbit missions (Shaver et al., 2003). However, passive shielding alone is 1) insufficient in blocking the high penetrance of HZE particles, 2) unable to prevent spallation from occurring as particles collide with shielding materials, and 3) impractical in exploration mission designs due to limited lift-mass capabilities (Clowdsley et al., 2005). Ferrone et al. (2021) proposed the addition of active shielding using superconductors and found that generating high-strength magnetic fields (7 Tesla) could meet NASA exposure limits for long-distance long-duration space flights. However, Bamford et al. (2011) published a patent demonstrating that a significantly lower $1\times10^{-4}$ Tesla strength magnet would be sufficient to filter out most of the background space radiation existing in our galaxy. The magnetic field would, however, be weakened by the opposing cosmic background magnetic field which permeates the galaxy and is believed to be amplified by the spiral motion of the milky way (Zhang et al., 2022). Gunn (2022) cites NASA's Planetary Science Division which contends that by increasing the field strength to 0.1 – 1 Tesla, the magnetic shield would generate a size of about 100-200 m across (Bamford et al., 2022). Bamford et al. (2022) assert that the 0.1 – 1 Tesla shield would also be strong enough to repel the background magnetic field and generate a sufficient boundary layer between the spacecraft and space radiation.

Active magnetic shielding blocks the transmission of particles and electromagnetic waves, and its effectivity is a function of the shield material's thickness and conductivity. Shielding interactions with charged particles differ from their interaction with electromagnetic waves. For particles, the magnetic shield strips electrons away from the particle and results in a dipole moment. The resulting change in charge then acts as a driving force that deflects the original particle (Ferrone et al., 2023). When an electromagnetic wave encounters the shield: 1) much of the energy is reflected and refracted away from the ship, and 2) the residual energy is then absorbed by the shield which ultimately reduces the magnitude of energy from the particle or wave (Ferrone et al., 2021). Active magnetic shielding has already been identified for further study due to its high effectiveness in NASA's Magnetospheric Dipolar Torus (MDT) project (Shepherd et al., 2009) and CERN's Space Radiation Superconducting Shield (SR2S) project (Bruce et al., 2015). Several configurations have already been designed; all of which proved to be successful in models (Ferrone et al., 2021). However, severe drawbacks to active magnetic shielding exist. Firstly, magnetic field models predict magnetic field strengths that require large sources of energy to generate and maintain (Ferrone et al., 2021). Additionally, high magnetic field strengths risk damage to the sensitive electronics aboard the vessel (Ferrone et al., 2021). In summary, creating a magnetic field that is strong enough to deflect HZE particles but weak enough to not harm electrical equipment is still limited to theoretical design and has not been tested in the space environment. Despite these challenges, active magnetic shielding represents one of many potential countermeasures under development for safe future space travel.

## The Repurposing of Personalized Therapies

Aboard the ISS, astronaut crew members are at the privilege of regular medicine resupply schedules, medical equipment, and reliable communication with health professionals on the ground. However, the advent of longer missions beyond low Earth orbit escalates the risk of health emergencies via prolonged exposure and the diminishing of medical resources (Komorowski et al., 2016). Delays in communication and medical asset supply lines further reduce the efficacy of current intervention methods that rely on ground medical resources. Furthermore, as much as one-third of medications do not work as intended depending on the individual (Spear et al., 2001). Individual response variability to medication efficacy and toxicity can slow treatments and waste precious medical resources in adverse situations. It is thus imperative that personalized strategies be adopted for individual astronauts to minimize reliance on ground-based intervention strategies and avoid treatment failure.

Genetic variations in astronauts change individual responses to spaceflight environmental factors including health risks and treatment responses (Spear et al., 2001). In response to inter-individual variability, personalized therapies are being extensively studied by public and private space entities to address the many hazards of space (Iosim et al., 2019). Taking inspiration from regenerative medicine and immunology, established cellular therapies are being repurposed to protect astronauts. Iosim et al. (2019) list multi-omic analyses, next-generational sequencing, personalized antibiotics, and individual dietary order to be the most important techniques for translating pharmaceutics and therapies in space. The many possibilities of this approach address health changes across the entire body. For example, the similarities between neurological diseases and spaceflight-induced CNS impairments could lead to the repurposing of pre-existing FDA-approved medications through computational modeling (Nelson et al., 2019). Additionally, metabolic disorder medicines can be repurposed to limit the overproduction of reactive oxygen

species and improve the mitochondrial health of astronauts. Therapies such as Resveratrol have strong antioxidant properties through the coactivation of the SIRT1 gene which regulates cell inflammation and stimulates mitochondria biogenesis and cell/tissue repair (Bhatti et al., 2017). Personalized therapies should also be applied to ensure effective diagnosis and treat emergent health effects during space flight. This approach requires reliable diagnostic tools to select optimal treatment options for specific individuals. One concept is in the cataloging of cellular avatars – or the creation of virtual cell models unique to each individual's genetic predisposition (Goetz & Schork, 2018). Cellular avatars enable effective drug screening through machine learning prediction models, which circumvents the time- and resource-consuming 'trial-and-error' approach (Durinikova et al., 2021).

Additionally, strength and resistance training mitigate muscle and bone loss for astronauts aboard the ISS (Smith et al., 2012). The rationale behind these exercises lies in the gradual loading of/adding weight to the bone as a mechanical stimulus for increasing bone mineral density and muscle growth. The efficacy of these exercises depends on the intensity of the training at high loads over longer periods (Benedetti et al., 2018). Because muscles and bone tissue are both metabolically active and have high turnover rates which change depending on the environment, mineral resorption and density loss are increased during spaceflight regardless of exercise. This results in calcium imbalances which also increases the risk of kidney stones (Smith et al., 2015). Thus, medical therapies in combination with strength and resistance exercises are proposed to mitigate harmful bone and muscle health changes. For example, the repurposing of supplements inclduing calcium, omega 3, and vitamin K is being studied to reestablish calcium equilibrium in the body (Smith et al., 2015). Oxidative stress, which is also

linked to bone and muscle health, makes the adoption of antioxidant supplements a compelling possibility for bone and muscle preservation (Tian et al., 2017).

## Limitations in Studying Space Health Risks

Despite numerous studies on the spaceflight environment, understanding the risk posed to health in long-duration missions remains limited. Space health studies struggle to understand actual health effects because of the wide range of factors limiting the replication of the spaceflight environment and its effects on humans (Simonsen et al., 2020; Williams et al. 2010). Specifically, the challenges of emulating radiation in the spaceflight environment and the choice of surrogate animal models have all limited efforts to expand human spaceflight.

### Simulating the Space Environment

Terrestrial spaceflight simulations are crucial to the development of effective countermeasures. However, some hazards are comparably more difficult to emulate than others. One of the primary means of studying health responses during spaceflight is through replicating GCR at particle facilities on Earth. $^{60}$Co gamma rays are used as the standardized model for all forms of radiation and have the relative biological effect (RBE) value of 1, which all other radiation tests are normalized to this value (Zeman, 2016). An RBE = 1 means the biological effect of the test radiation is as effective as $^{60}$Co; an RBE < 1 means that the test is less effective and vice versa for RBE > 1 (Zeman, 2016). However, the mechanism of energy transfer and subsequent biological damage from space radiation is different from terrestrial analogs such as $^{60}$Co due to ionizing vs. nonionizing and direct ionization vs. indirect ionization properties (Dertinger et al., 1970). This means that charged particles with varying atomic weights are

compared on a scale designed for photons and uncharged small particles. Thus, this standard of measuring dose and risk of exposure introduces limitations when attempting to understand complex radiation environments in space.

Another limitation to simulating the space environment is in dose delivery. Most research on space radiation health risks has been accomplished by exposing mouse models to cumulative mission doses of single-ion, mono-energetic beams over short periods (Simonsen et al., 2020). However, the space environment consists of multiple ion species over a broad energy range, and space missions (hence radiation exposure) are expected to occur over months if not years (Simonsen et al., 2020). These study guidelines are flawed as they ignore essential biological responses expected under chronic, low-dose radiation states such as upregulation of DNA and cell/tissue repair operations. Furthermore, acute biological responses reported by these acute exposure studies are unlikely to occur from GCR dose rates in space (Kennedy et al., 2014).

To address dose delivery limitations, NASA developed a GCR analog that can deliver multiple mono-energetic ion beams in a succession of one another (Simonsen et al., 2020). The NASA Space Radiation Laboratory (NSRL) can generate heavy ions – C, O, Si, Ti, and Fe – found in the GCR spectrum at individual beam fractions as low as 0.1 to 0.2 mSv and over 2 to 6 weeks (Simonsen et al., 2020). Despite clear improvements and great strides being made in terrestrial GCR analogs, this simulator is still limited in the capability of truly replicating the spaceflight environment. For example, the NSRL is unable to generate post-spallation subatomic particles such as pions and neutrons that reportedly make up to 15–20% of the total radiation dose for astronauts (Norbury et al., 2016; Slaba et al., 2015). Additionally, the NSRL utilizes consecutive ion exposure as opposed to the simultaneous exposure of multiple ions of the actual radiation environment. Experimental results also potentially change depending on the order of

ions delivered, resulting in disagreement on the suitable sequence of mixed ion beam delivery (Elmore et al., 2011; Norbury et al., 2016). Elmore et al. (2011) observed changes in preneoplastic to neoplastic phenotype transformation in mice depending on changes to radiation exposure protocols including 1) the time interval between mixed ion beam exposure and 2) the sequential order of 1 GeV iron ions and 1 GeV protons. Varying interval and order, phenotype transformations were mostly similar amongst all protocols except for the specific case of 10 cGy iron ions followed by 1 Gy protons in immediate succession (Elmore et al., 2011). The resulting difference in tissue transformation suggests that single ion beams may be limited in replicating certain experiments that are dependent on ion order.

## Animal Models as Human Analogs

While animal models have been invaluable surrogates in obtaining data that would not otherwise be ethically gained from human research, they pose many challenges in reliability as accurate analogs due to numerous differences in anatomy, metabolism, and genotyping between humans and other animals. (Williams et al. 2010). The most common animal models are rodents, such as mice and rats. Especially because of sanctions on animal protection and sentimentality, significantly fewer studies utilize larger mammals including non-human primates. (Williams et al. 2010). Despite mouse models' significant contribution to radiation risks and mechanisms of disease, their capability in predicting human health is controversial due to limiting differences in dose distribution across the body and dose fatality.

In small animal models, such as mice, radiation exposure is scaled down in proportion to their smaller size. However, the scaling down of particle energies significantly changes the LET of particles and produces experimental results different from that expected of larger subjects

(Cengal et al., 2010). In contrast, not scaling particle energy down leads to altered distributions of exposure that are aggregated in the internal organs (Cengal et al., 2010). Using larger animal models would solve this issue, allowing for a more representational LET spectrum to that of humans without altering dose distribution, providing more robust predictions of human health responses (Cengal et al., 2010). There is, however, further uncertainty on if and how health effects may be altered depending on the variations in animal species (Williams et al. 2010).

Further differences between human and animal model responses to radiation are indicated by differences in radiation resilience. Radiation-induced death is represented by $LD_{50}$ or the immediate lethal dose required to kill half the members of a tested population. $LD_{50}$ is different between different species, and the basis for interspecies variation in radiation dose tolerance is not fully understood (Hall and Garcia, 2018). Mouse animal models have been the most extensively used analogs to study human diseases, including those linked to radiation. However, in addition to their different physiology related to size, mice (mouse $LD_{50} = 8.16$) have significantly higher $LD_{50}$ and radiation tolerance than larger mammals such as humans (human $LD_{50} = 3.5$) (Hall & Garcia, 2018). In addition to size, interspecies $LD_{50}$ variation is believed to be due to different mechanisms of death at fatal dose limits for different animals (Lorenze & Congdon, 1954). For larger mammals, the cause of death at fatal doses of radiation is reported to be because of the destruction of blood precursor cell lines and the failure of the hemopoietic system. Either interorgan hemorrhage caused by over-coagulation or infection caused by the handicapping of the immune system predominates as a physiological response to fatal radiation exposure (Krigsfield et al., 2014; Lorenze & Congdon, 1954). Both reactions predate declines in platelet counts postexposure. Following $LD_{50}$ fatal dose exposure, larger mammals including humans exhibit hemorrhage upon mortality. In contrast, mouse models do not undergo

hemorrhaging of the organs but instead exhibit bacterial infection leading up to organ failure (Boone et al., 1956). Overall, these results suggest that human responses to fatal doses of radiation differ from mouse models and beg the question if this trend remains consistent with nonacute GCR radiation risks.

## Conclusion

The limited study of astronaut health has yet to provide an accurate estimate of cumulative risk, not to mention reliable prediction methods or countermeasures in response to space radiation health hazards. In preparation of future missions beyond low Earth distances, there first needs to be a deeper understanding regarding risks and health changes. In particular, the combination of ground and space studies through multi-omics analysis could be the strategy needed to translate spaceflight scenarios to space radiation knowledge. Expanded use of the animal and cell laboratory aboard the ISS in conjunction with ground-based studies could enable the selection of potential surrogates as human analogs. Longitudinal health studies using machine learning models could further analyze the connection between symptoms of rapid aging and the radiation environment. Furthermore, the advancement of whole genome sequencing and multi-omic analysis of the cellular response could enable the prediction of drug efficacy and disease susceptibility in individuals. Thus, multivariable investigations open new opportunities to assess space radiation risk on the genomic level and identify potential biological targets for deeper analysis. Only through the integration of sufficient data to first understand space radiation-associated risk can the development of detection methods and protective countermeasures truly hasten humanity's next steps in space exploration.

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# Author Biography

Bill Xu Tang is a graduating senior at the University of Texas at Austin pursuing Biochemistry through the Polymathic Scholars Honors Program. Bill's love for space and admiration for medicine arose from growing up in a household embattled with cancer. His favorite hobby of stargazing through his telescope gave him the drive to overcome some of life's earliest challenges. Bill will pursue a career in medicine with dreams of someday treating patients in outer space.