Space Radiation Book Chapter

Health Impacts of Radiation in Space and Countermeasures

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Abstract
Space radiation poses one of the most significant health risks for long-duration space missions, with cancer, cognitive decline, and cardiovascular issues among the primary concerns (Patel et al., 2020). Since the Apollo mission, the biological effects of space radiation on humans and the linked specific mechanisms remain incompletely understood, with no direct evidence linking space radiation exposure to specific health outcomes in astronauts with two notable exceptions: reduced latency to cataract formation and light flash phenomena experienced during Apollo missions and South Atlantic Anomaly crossings. As humanity prepares for ambitious missions to the Moon, Mars, and beyond, mitigating the long-term risks associated with galactic cosmic radiation (GCR) and solar particle events (SPE) is crucial. This chapter explores the latest findings on space radiation effects on human health and highlights the current knowledge gaps in human space radiation biology. Lastly, this chapter discusses emerging countermeasures that may help safeguard astronaut health in future deep-space missions. As NASA and other space agencies venture into deep space, it is critical to balance the promise of gene-editing interventions with their societal and ethical implications, particularly when these space-faring humans return to Earth or in the context of generational effects. Hence, we hope to shed some light by evaluating the feasibility and acceptability of such interventions, ensuring that future countermeasures align with both mission objectives, ethical standards, and the well-being of space explorers.

Part 1: The Space Radiation Environment

In view of manned missions targeting the Moon and Mars, it is essential to understand how the deep space, Lunar and Mars radiation environment impacts biological processes in the human body. The space radiation environment is vastly different from the radiation environment experienced on Earth, and comprises a complex mix of high-energy protons, helium ions and heavy ions from GCR, gamma rays, and streams of protons and electrons from solar particle events (SPE), and particles trapped in the Earth's magnetic field, the radiation belts (Van Allen belts) (Nelson, 2016). Their combined influence, along with interactions with spacecraft, equipment, space suits, or planetary regolith, shapes the radiation environment encountered by the astronauts.

1. Galactic Cosmic Rays

GCR are high-energy particles originating from outside our solar system, predominantly from within the Milky Way galaxy. They consist mainly of fully ionized nuclei, with approximately 85% being protons, 14% helium nuclei or alpha particles, and the remaining 1% comprising higher elements and a small fraction of electrons. The energy spectrum of GCR spans several orders of magnitude, ranging from tens of MeV to beyond 10^{20} eV. This broad energy range allows many GCR to penetrate shielding, exposing astronauts to a constant low dose rate of a complex radiation field, posing significant challenges for space exploration and potential health issues to astronauts (Chancellor et al., 2018; Guo et al., 2022; Kokhan and Dobynde, 2023).

The origins of GCR are attributed to astrophysical phenomena such as supernovas, which accelerate particles to relativistic speeds through mechanisms like shock wave acceleration. Once accelerated, these particles propagate through the interstellar medium influenced by galactic magnetic fields that cause them to follow complex, diffusive trajectories (Castellina and Donato, 2013).

Upon entering the heliosphere, GCR encounter the solar wind and the Sun's magnetic field, which modulate their intensity. This modulation is anti-correlated with solar activity; during periods of high solar activity, the increased solar wind and magnetic field strength provide a greater shielding effect, reducing GCR flux, and vice versa during solar minima (Potgieter, 2013). The interaction of GCR with Earth's atmosphere leads to the production of secondary particles through a cascade of nuclear interactions known as air showers (Mironova et al., 2015). These secondary particles contribute to background radiation levels on Earth's surface and can influence atmospheric chemistry and cloud formation (Polatoğlu and Gül, 2024).

During human spaceflight, GCR are a major concern due to their potential biological effects that increase long-term health risks (Chancellor et al., 2014). HZE ions in particular are characterized by a high linear energy transfer (LET), meaning they deposit dense tracks of ionization along their paths through tissue (Chancellor et al., 2014; Cucinotta et al., 2006; Cucinotta and Durante, 2006; Durante and Paganetti, 2016; Simonsen et al., 2020). This can result in complex biological damage, increasing the risk of carcinogenesis, central nervous system (CNS) effects, and other degenerative diseases (Cucinotta et al., 2014; Durante and Cucinotta, 2008; Simonsen et al., 2020). The high penetration capability of GCR makes shielding challenging, as traditional materials cannot effectively attenuate their energy without generating secondary radiation (Slaba et al., 2016).

Research is ongoing to develop effective countermeasures against GCR exposure, including advanced shielding materials, gene therapy, or pharmacological interventions, as we will discuss later in this chapter. Understanding the composition, energy distribution, and propagation mechanisms of GCR is essential to define the space radiation exposure for assessing the risks, developing mitigation strategies, and planning future deep-space missions (Kokhan and Dobynde, 2023).

2. Solar Particle Events

SPEs are another significant source to the radiation environment in space. Coronal mass ejections (CME) release particles, predominantly protons, along with electrons, alpha particles, and heavier ions, also known as Solar Energetic Particles. This broad cloud of charged particles is typically confined within a magnetic field which expands and travels through the solar system, at speeds that can vary from 200 km/s up to 2,000 km/s. CME typically takes 2-3 days to reach Earth, while occasionally they may take less than 24h (NASA, n.d.). CME can occur concurrently with solar flares, creating giant bursts of energetic electromagnetic waves traveling at the speed of light, reaching the Earth within 8 minutes. Both types of events are formed as the result of the twisting and realignment of the sun's magnetic field, a phenomenon known as magnetic reconnection (Hu, 2017).

Spatially, SPEs can have an extensive reach, with some events being detected across a wide range of heliolongitudes (Dresing et al., 2023). The frequency and intensity of SPEs are modulated by the solar cycle, an 11-year cycle of solar magnetic field reversal, exhibiting a higher occurrence rate during periods of solar maximum. However, significant events can occur during any phase of the solar cycle (Papaioannou et al., 2016), making prediction challenging.

While most SPEs pose minimal risk to astronauts due to their low energy, early warning systems, and available protective measures, large, high-energy SPEs - though rare (Zeitlin et al., 2013) - can be hazardous, in particular if astronauts are exposed during extravehicular activities (EVA), in free space, or during planetary operations. SPEs having high fluence of protons with energies above 30 MeV are of particular concern for EVAs, as these particles can penetrate EVA spacesuits and result in acute radiation syndrome (ARS) (Carnell et al., 2016). Mitigation strategies for SPE-induced hazards rely on forecasting, real-time monitoring, and the development of advanced shielding materials. Predictive models aim to provide early warnings, allowing mission control to delay, abort, or cancel EVA when necessary. In spacecraft, dedicated "storm shelters" with additional shielding help reduce radiation exposure during large SPEs (Townsend et al., 2018). Long-duration vehicles such as the Mars Transit Habitat may incorporate permanently shielded areas, while smaller vehicles such as Orion require astronauts to configure onboard components to enhance protection.

3. Secondary Radiation

Secondary radiation is a cascade of particles generated when primary cosmic rays, mainly GCR, interact with spacecraft materials, planetary surfaces, or even the human body. Previous research has demonstrated that the interaction of energetic protons and HZE nuclei with spacecraft structures can produce an additional intra-vehicular radiation hazard (Cucinotta et al., 2006; Norbury et al., 2016; Wilson et al., 1999; Zeitlin et al., 2013). These nuclear interactions produce a spectrum of secondary particles, including neutrons, charged particles, pions, and muons, which contribute to the overall radiation environment encountered by astronauts (Slaba et al., 2016; Wilson et al., 1991).

The generation of secondary radiation is a significant concern for space missions, as it can enhance the radiation dose beyond that contributed by primary particles alone (Norbury and Slaba, 2014; Wilson et al., 1995). These secondary particles can possess substantial energy and penetrate deeply into biological tissues, potentially causing damage at the cellular and molecular levels (Cucinotta et al., 2013b). The health implications of secondary radiation are profound, as secondary particles, particularly neutrons and heavy ions, can have high LET properties.

Spacecraft shielding is optimized in terms of material composition and thickness to mitigate the cumulative biological effects of both primary space radiation and the secondary particles produced through interactions with the shielding itself, both in terms of material and thickness, to minimize the production of secondary particles (Loffredo et al., 2023). However, this is a complex task, as introducing thick shielding can lead to the buildup of secondary particles that increase the dose equivalent (product of absorbed dose in tissue multiplied by a quality factor) compared to free space. For instance, an optimum thickness of 20 g/cm^2 is obtained for aluminum shielding, a thickness beyond which additional thickness results in the build-up of secondary particles (mainly protons) and increases the dose equivalent (Slaba et al., 2017). These properties are material-dependent, with hydrogen-rich materials (e.g., polyethylene) showing a steady decrease of the dose equivalent with increasing shielding thickness. Importantly, shielding strategies are limited by spacecraft launch cost constraints. Thus, material selection and structural design are critical in developing effective radiation protection strategies for astronauts.

4. Lunar Frontiers: Understanding the Radiation Challenge for NASA's Artemis Mission

The Lunar radiation environment is the same as the deep space environment (De Angelis et al., 2007) with two exceptions: a. lunar radiation is half omnidirectional, with the mass of the moon shielding approximately half of the deep space radiation, resulting in less severe exposure than in deep space; b. GCR interact with the lunar regolith, creating albedo neutrons through nuclear interactions (De Angelis et al., 2007). Neutrons scatter omnidirectionally and can be created a few meters below the lunar surface. Although the albedo neutron spectrum may appear to rise at low energies, the actual number of neutrons at very low energies (E < 10 KeV) is relatively low in space environments. Most neutrons remain in the intermediate to high energy range, with some reaching to hundreds of MeV. While individual high-energy neutrons may have a lower relative biological effectiveness, they can produce secondary particle cascades that amplify the overall biological risk. The estimates of the contribution of albedo neutrons to exposure varied between 1-32% for SPEs and 7-27% for GCR environments, depending on shielding conditions (habitat material and thickness), and SPE energy spectrum (Slaba et al., 2011). Hydrogen-rich materials can be used in the floor of a habitat to mitigate the albedo neutron exposure. While other secondary particles (e.g., photons, electrons, etc.) are produced at similar rates, their contribution to surface-level exposure is smaller because charged particles are more effectively attenuated by the regolith, unlike neutrons, which can travel from deeper layers to the surface.

The Artemis program consists of several phases during which astronauts will be exposed to different levels of radiation. The encountered space radiation environments include short traversal through the Earth's radiation belts, extensive journey in the lunar Gateway (space station in lunar orbit) where the space radiation environment is that of the free space modified by shielding, and exposure to the lunar environment during operations on the lunar surface (NASA, 2020; Werneth and Huff, 2025). Dose estimates vary depending on the mission duration, from 70 mSv for a short, 42-day lunar surface mission up to 300-400 mSv for an extended, 1-year lunar mission, compared to 500-650 mSv for a 1-year mission to the lunar Gateway (Werneth and Huff, 2025), depending on shielding assumptions and solar cycle conditions.

For context, the average annual radiation dose for a person on Earth from natural sources is about 2.4 mSv (Mc Laughlin, 2015), while a computed tomography (CT) scan of the abdomen delivers approximately 10 mSv. Extended space missions expose astronauts to radiation levels that approach or exceed the current NASA career exposure limits, which are set based on estimated risks of radiation-induced cancers and other adverse health effects.

5. Cosmic Perils: Understanding and Addressing Radiation Risks for Mars Exploration

Similar to the lunar surface environment, the Mars' radiation environment poses a significant challenge for human exploration due to its lack of a global magnetic field. Unlike the Moon, Mars possesses a thin carbon dioxide atmosphere, varying from 15 to 25 g/cm^2 depending on Mars' surface topology, further modifying the space radiation environment. While the thin atmosphere can stop a significant fraction of SPE, it is unable to stop a significant proportion of GCR (Guo et al., 2021). Secondary radiations are also a concern, as these high-energy particles interact with the atmosphere, producing a radiation environment that is different to that of free space, with secondary neutrons being especially a concern for radiation protection (Slaba et al., 2013). Natural geological structures may be used as radiation shelters against intense SPE and as a strategy to limit exposure to continuous GCR.

While the Mars mission architecture remains to be fully conceptualized, significant exposures will arise during the transits to and from Mars, as well as during the stay on the surface of Mars. Measurements obtained by NASA's Mars Science Laboratory's Radiation Assessment Detector (MSL-RAD) on the Curiosity rover were 1.84 mSv/day in transit and 0.7 mSv/day on the Mars surface (Zeitlin et al., 2013). Mars missions' estimates vary from 870-1,200 mSv for mission duration between 650 days (conjunction class

short days: 620 days free space and 30 days surface) and 920 days (opposition class long stays: 420 days free space, 500 days surface) (Simonsen et al., 2020). Considerable variation is expected in these estimates, depending on the timing of the solar cycle, the frequency of SPEs, and shielding strategy.

Part 2: Effect of Space Radiation on Cellular and Organ Systems

Decades of ground-based radiobiology and epidemiology research have identified many cellular and organ systems at risk of radiation-induced adverse health effects. This section provides an overview of the current strategies utilized to characterize them in the context of space radiation exposure. An overview of cellular and organ systems that are at risk of space radiation-induced decrements is then provided in three sections, based on the degree of evidence from pre-clinical data and epidemiology studies.

1. Current Strategies to Characterize Space Radiation Health Decrements

With the space-radiation environment being fundamentally different from terrestrial exposures in terms of radiation quality, dose, and dose rate, characterizing the health consequences of space radiation exposure is challenging. The astronaut cohort is, to date, too small to derive excess relative risks due to space radiation exposure, which occurs in the presence of many other environmental factors. Current strategies rely on epidemiology studies of radiation-exposed human cohorts and pre-clinical data from cellular and animal models to supplement knowledge gaps from epidemiology studies.

The Life Span Study, which investigates radiation-induced health effects for survivors of the Japanese atomic bombs, is one of the most comprehensive radiation epidemiological studies of the effect of radiation on humans (Grant et al., 2017) and is currently used in the NASA cancer risk model to derive excess radiation-induced hazard rates (Cucinotta et al., 2013b; Simonsen and Slaba, 2021). However, atomic bomb survivors were primarily exposed to acute doses of low-LET gamma rays with a smaller neutron component, exposure that is substantially different from what astronauts will experience during space missions beyond LEO. There is limited human data for the effects of high LET radiation exposure, and the effect of low dose and dose rate exposure, compared to acute exposure, is still debated. For high LET, radon gas alpha particles in the lungs of uranium miners and some internal emitter data from nuclear waste exist, but in these cases, the radiation source is internal, and subsequent dose distributions are very different from those of deep space radiation exposures. Although radiotherapy with protons and carbon ions is increasingly routine, these treatments involve localized high-dose exposures that, as for internal emitters, do not replicate the chronic, whole-body exposures experienced in space. They also involve cohorts of patients undergoing cancer treatment, cohorts that are very different from the healthy astronaut population. More recently, a comprehensive epidemiology study called the “Million Person Study” (Boice et al., 2022) has assembled data from 29 available cohorts of American persons totaling over 1 million who were exposed to low LET and high LET radiation from as early as 1939, providing new epidemiological insights into the effect of radiation that will complement current cancer risk models and extend to other long-term health risks, such as neurodegenerative and cardiovascular diseases.

As the majority of human epidemiological data and pre-clinical data are available for acute, low LET exposures, current strategies to estimate space radiation risks rely on data from low LET exposures in humans supplemented by animal studies to account for higher LET and low dose rates. Historically, cellular and animal datasets used acute doses of monoenergetic ion beams, reflecting the limitations of early accelerator technologies, which primarily produced single-energy particles. These datasets provided valuable insights into how radiobiological endpoints vary with regard to particle type and energy. These mono-energetic exposures are different from the complex, mixed radiation field that astronauts are exposed to. It remains unclear whether exposure to such a complex radiation field will result in additive effects or some synergistic effect between the different radiation types that might further increase the risks (Huff et al., 2023). NASA’s cancer risk projection models incorporate these uncertainties. The current model estimates a relative uncertainty of approximately 260% (Cucinotta et al., 2021), reflecting the

limitations of extrapolating from low-LET data and simplified radiation environments. To refine these projections, recent efforts have explored ensemble modeling approaches that integrate multiple plausible risk models (Simonsen and Slaba, 2021). For Artemis mission exposures, individual models within the ensemble framework have produced mean cancer risk projections differing by a factor of two or more, highlighting the challenges in defining a central estimate grounded in available epidemiological and radiobiological data. To further understand the effect of mixed field exposure and dose rate effects, NASA has developed the "Galactic Cosmic Ray simulator" (GCRsim) at the NASA Space Radiation Laboratory (NSRL) at Brookhaven National Laboratory (BNL), which mimics a reference radiation field, defined as the radiation environment found within the blood-forming organ of a human (body-averaged surrogate) behind 20 g/cm^2 of aluminum shielding during solar minimum (Simonsen et al., 2020), encompassing both primary and secondary (GCR interactions with spacecraft and tissue) radiations. The GCRsim consists of a total of 33 energetic ion beams that collectively cover a broad range of particle types, energies, and LET that can be delivered either acutely (~ 75 minutes for 500 mGy exposure) or chronically in multiple small exposures over several weeks. Future studies utilizing the GCRsim should allow further understanding of the effect of mixed beam and low dose-rate exposures for multiple biological endpoints. This space radiobiology research platform will also enable the testing of possible countermeasures to mitigate radiation-induced health risks.

2. Established Effects of Space Radiation on Cellular and Organ Systems

2.1 DNA, a Central Target of Space Radiation for Carcinogenesis

Since the discovery of the DNA structure in the 1950s, decades of radiobiology studies have demonstrated the central role of DNA in radiation-induced biological outcomes, such as cell death and carcinogenesis. Ionizing radiation creates DNA lesions by ionizing or exciting atoms of the DNA (direct effect), or by ionizing or exciting water molecules in the vicinity of the DNA, generating highly reactive free radicals that diffuse and can react with the DNA structure, causing additional damage (indirect effect) (Baeyens et al., 2023; Bailey et al., 2024; Cornforth et al., 2023; Eidemüller et al., 2023; Loucas et al., 2022; Reindl et al., 2023). These processes result in DNA strand breaks or base lesions triggering the DNA damage response, which attempts to repair the lesions and restore the DNA integrity by recruiting multiple proteins (Bailey et al., 2024). Among these lesions, DNA double-strand breaks (DSB), which occur when two strand breaks form on opposite strands within ~ 10 bp, can form chromosome aberrations when misrepaired, including mutations such as reciprocal translocations, inversions and small deletions (Bailey et al., 2024). Cells harboring non-lethal aberrations can sustain these structural changes and pass them to descendent cells (Cornforth et al., 2023; Loucas et al., 2022). This might play a key role in radiation-induced carcinogenesis, which is currently thought as a result of a multi-stage process where cell initiation (acquisition of competitive advantage, e.g., mutation) and/or promotion can be enhanced by radiation (Eidemüller et al., 2023). Carcinogenesis remains one of the major radiation-induced long-term health risks for missions beyond LEO. The risk of radiation-induced cancer incidence and death has been well characterized by epidemiology studies for low LET radiation ("The 2007 Recommendations of the International Commission on Radiological Protection. ICRP publication 103"), particularly the Life Span Study. Carcinogenesis is extensively covered in a different chapter of this book. In this section, the focus is on a biological surrogate endpoint - chromosome aberrations - that have been used to estimate radiation quality and dose rate factors, and could be used to assess individual radiosensitivity or test countermeasures.

Compared to low LET radiation, high LET particles such as HZE ions induce particularly complex DNA lesions. Due to their high ionization density, HZE ions can generate complex DNA DSB, where many DNA lesions (strand breaks, base damage) occur in close proximity (within less than 10 bp), making repair more challenging (Van Der Schans, 1978). Additionally, HZE can induce multiple DSBs along ion tracks (Desai et

al., 2005), favoring misrepairs and the formation of complex chromosome exchanges. Extensive *in vitro* studies of aberrations in human blood lymphocytes and fibroblasts have demonstrated a strong dependence of chromosome exchange incidence on LET, and have provided valuable carcinogenesis surrogate data to assess radiation quality of high LET radiation (George et al., 2003, 2015; K. A. George et al., 2013a; Hada et al., 2014). Cytogenetic data, including chromosome aberrations, have also been proposed to assess dose and dose rate effectiveness factors for low LET exposures (Trabalka et al., 2017).

Cytogenetic biodosimetry using the blood lymphocytes of astronauts has been proposed as a tool to evaluate individual biological responses of astronauts to space radiation exposure (K. George et al., 2013). The radiation sensitivity of blood cells, especially lymphocytes, and the easy availability of blood samples make chromosome aberrations a potentially useful tool to evaluate astronauts' personalized risks of cancer incidence. Multiple studies measuring blood lymphocyte aberrations in astronauts, including dicentrics (Obe I. Johannes C. Johannes K. Hall, 1997; Testard , M. Ricoul , F. Hoffschir, 1996, 1996), translocations (Cucinotta et al., 2008; George et al., 2005; Yang et al., 1997) and inversions (Luxton et al., 2020), showed measurable differences pre-flight compared to post-flight for missions of a few months or more, provided blood was collected within a week or two of return from space. A number of studies organized by K. George, F. Cucinotta et al. used fluorescence *in situ* hybridization (FISH) to quantify chromosome exchanges in crew members' blood before and after spaceflights of duration up to 4 months and correlated the observed incidence with in-flight radiation exposures (George et al., 2010, 2007, 2005, 2001) and ground based calibrations (Feiveson et al., 2021). Frequencies were elevated after flight, especially at the 1-month time point, but gradually declined, and when assessed for up to 5 years postflight revealed half-lives of 10 - 58 months. The investigators conclude that cytogenetic biodosimetry is practical, takes into account the interactions of radiation and other spaceflight environmental factors that can affect physiology, and can be used to validate models for radiation-carcinogenesis which have a DNA damage component (K. A. George et al., 2013b) despite complications from high LET radiation effects on cell cycle delay. Inversions measured by directional genomic hybridization have also been proposed as a tool for retrospective radiation exposure (Ray et al., 2014). While current risk estimates rely on epidemiological data, chromosome aberration biodosimetry derived from astronauts' blood cells reflect individualized responses to radiation exposure and could play a key role in providing personalized risks to radiation exposure, improving communication of long-term health risks for individual astronauts to support informed consent (Committee on Assessment of Strategies for Managing Cancer Risks Associated with Radiation Exposure During Crewed Space Missions et al., 2021). Current NASA permissible exposure limit was fixed at 600 mSv for all ages and sexes based on NASA cancer model (NASA, 2023).

2.2 Mitochondria, Another Cellular Target of Space Radiation

While the cell nucleus is clearly an important target for radiation-induced damage, recent studies have highlighted the importance of other cell structures, especially mitochondria, which regulate metabolism, oxidative stress, programmed cell death (apoptosis), and are affected by radiation. Radiation exposure in space directly impacts mitochondrial function through multiple mechanisms. Beyond nuclear and mitochondrial DNA damage, radiation disrupts the mitochondrial respiratory chain, leading to an increase in reactive oxygen species (ROS) production, which impairs mitochondrial function (Yamamori et al., 2012; Yatagai et al., 2019). These stress responses, first observed in plants (Porterfield et al., 1997), have now been confirmed in humans through a NASA GeneLab multi-omics analysis, which showed widespread mitochondrial stress in spaceflight samples (da Silveira et al., 2020; Guarnieri et al., 2025). However, the exact relationship between radiation and other factors contributing to mitochondrial damage, like microgravity, remains unclear.

Radiation-induced damage to mitochondria also involves phospholipid destruction and peroxidation, a well-established mechanism of radiation harm (Ye et al., 2020). This damage extends to other organelles such as chloroplasts and peroxisomes (Su et al., 2022). The best descriptions of mitochondrial radiation responses come from oncology and cancer therapy, demonstrating that radiation exposure leads to stress-induced ROS release (Kim et al., 2019). Mitochondrial stress in space is not only driven by radiation but also by factors like hypoxia and hypercapnia, which contribute to anemia and decreased aerobic capacity during long-duration space missions (Kunz et al., 2017). To better understand mitochondrial stress in space, it is crucial to differentiate the impacts of microgravity and radiation. This distinction provides a foundation for developing more accurate biophysical models of life in space, advancing our knowledge of how spaceflight affects living systems.

2.3 Solar Particle Events and Acute Radiation Syndrome Risk

As previously mentioned, exposure to unshielded SPE, for instance during an EVA, or to shielded SPE with very energetic particle spectra (Zaman et al., 2021), could subject astronauts to large, acute doses that could affect multiple organs and lead to acute radiation syndrome (ARS).

Risks associated with such exposures have been reviewed elsewhere (Carnell et al., 2016; McPhee and Charles, 2009) and will be briefly summarized here. As for other risks, ARS evidence is based on ground-based observations of accidental acute, high dose exposures in humans, mostly for low LET radiation (X-rays, gamma-rays). Numerous national and international committees, such as ICRP (Clement et al., 2012) or NCRP (Griffiths, 1983; *Guidance on radiation received in space activities*, 1989; National Council on Radiation Protection and Measurements, 2000), have thoroughly documented the ARS symptoms. Multiple organs can be affected, but early effects (within hours to weeks after exposure) are mainly manifested in the hematopoietic, cutaneous, gastrointestinal, and neurovascular systems (Stewart et al., 2012). The development of ARS symptoms follows three phases, whose onset, duration and severity of symptoms are dose and dose rate dependent.

The initial symptoms are known as prodromal effects and include hematopoietic depression, gastrointestinal symptoms (nausea, vomiting, anorexia and/or diarrhea) and neurological symptoms (fatigue, thickness). The phase typically occurs within hours to a few days following exposure. The prodromal period is followed by a latent period, typically lasting 2 to 20 days, where the symptoms of the exposed person seem to improve. The last phase, known as the manifest phase, lasts from 2 to 60 days and is critical for radiation injury. Severe physiological symptoms appear due to the radiation affecting different organ systems. The main adverse health effects include (1) the hematopoietic syndrome (> 1 Gy) due to a drop in the number of blood cells that can severely compromise the immune system, (2) the cutaneous syndrome whose early symptoms (< 4 weeks) include erythema (4 Gy for 10% of the population to exhibit effect) and moist desquamation (14 Gy for 10% of the population to exhibit effect), and late symptoms include atrophy, fibrosis and/or necrosis; (3) gastrointestinal syndrome (> 4 Gy) due to the loss of intestinal stem cells and the inability to repopulate and maintain the epithelial barrier of the intestines, causing, in severe cases, infection, dehydration and electrolyte imbalances that can be life threatening; and (4) neurovascular syndrome whose late symptoms may include neurological and cognitive deficits, possibly due to cerebral edema, inflammation and endothelial damage to the microcirculatory system. Very high irradiation doses (> 6 Gy) can also cause permanent infertility. The lethality of the exposure is dose and medical care dependent (Anno et al., 2003). The estimated lethal dose 50 (dose is lethal for 50% of the population) from Nagasaki, where medical care was provided, is 4.1 Gy. The NASA dose limit to SPE events was fixed to be less than an effective dose of 250 mSv (NASA, 2023).

2.4 Space Radiation-Induced Cataract

Based on recent epidemiological studies of ocular exposure, the Main Commission of the International Commission on Radiological Protection (ICRP) stated in Publication 118 that the threshold dose for radiation-induced cataracts is now considered to be approximately 0.5 Gy for both acute and fractionated exposures (Bolch et al., 2013). This revised threshold is further supported by a growing body of experimental and clinical data. Cataract formation, a deterministic late effect of radiation, is characterized by posterior subcapsular lens opacification and shows an accelerated onset after radiation exposure, as shown in numerous rodent studies (Blakely, 2000; Young and Sutton, 2021). Radiation effects on molecular mechanisms for lens opacification have been studied in rodent and human cell cultures. It is estimated that a dose threshold of <0.8 Gy of low LET radiation can lead to cataract formation in humans (Blakely and Chang, 2007). (Cucinotta et al., 2001) conducted a historical review of health records and radiation dosimetry from 295 astronauts and found an increased cataract incidence for exposures > 0.8 mSv. (Chylack et al., 2012) further reviewed this relationship in the 5-year NASA cataract study and estimated a progression rate for lens opacification of 0.25 ± 0.13% lens area/Sv/year (P = 0.062). (Richardson, 2022) has further reviewed radiation-induced cataractogenesis and drawn attention to potential potentiation by elevated oxygen levels, which can be present in spaceflight. Finally, (Waisberg et al., 2024) have proposed in-flight monitoring of visual disturbances, including cataracts. The NASA dose limit for lens was fixed at 4,000 mGy-Eq for whole career exposure and 1,000 mGy-Eq for 30 day exposure (NASA, 2023).

3. Radiation Effects on Organ Systems: Rising Evidence

There is rising evidence linking space radiation exposure to potential organ-specific damage. While radiation has long been recognized as a major spaceflight hazard, recent ground studies - particularly those with high LET analogs and long-term exposure models - are strengthening this association in critical systems such as the CNS, cardiovascular system, and skeletal system (bone). Here, we highlight these organs as they may be especially susceptible to radiation-induced damage during prolonged space missions (Moon or Mars).

3.1 The Central Nervous System: A Target for Space Radiation-Induced Cognitive Impairments

There is limited knowledge regarding the acute and long-term effects of GCR on the CNS, which could contribute to deficits in behavioral performance. Human exposures have been limited almost exclusively to low LET radiation so animal models are critical in understanding any unique effects of high LET radiation exposure. Cucinotta et al., (2014) provide an overview of the risks posed by space radiation, particularly GCR, to the CNS. Over the last 20 years there has been significant progress in understanding the risks to the CNS from space radiation exposure which began with higher dose impacts on neurogenesis. The doses investigated have gradually reduced to levels commensurate with GCR doses expected on long term space missions (0.1 - 0.5 Gy) and outcome measures have expanded to include behavioral, electrophysiological, biochemical and gene expression measures in rodent models. There is still a need to translate findings through larger animal models to humans.

J. Fike and coworkers (Rola et al., 2005) initiated neurogenesis studies with charged particles and found reduced neural progenitor cell proliferation and differentiation in the hippocampus accompanied by increased pro-inflammatory cytokines and microglial activation, which are linked to cognitive impairments. (Rabin et al., 2009) began behavioral investigations with rats and charged particles in the mid 1980's which set the stage for more refined experiments as irradiation facilities improved and culminated in the NSRL at the BNL, which enabled high throughput studies with single ions or simulated

cosmic ray fields. Attention was drawn to space radiation effects on the brain in the 1970s when Apollo astronauts reported seeing structured light flashes during their lunar missions and confirmed by others on later missions. A number of combined electrophysiology and physics studies in space and on the ground by (Narici, 2008) have subsequently demonstrated that these visual illusions corresponded to the passage of individual particles through the retina or brain and may be associated with activation of rhodopsin in photoreceptors or by direct stimulation of neurons in optic chiasm or visual cortex. In a mouse model, (Sannita et al., 2007) showed that pulses of ^{12}C ions were able to generate prompt electroretinogram and visual cortex signals, suggesting direct depolarization of neurons from particle traversals. These observations demonstrate that radiation may modify perceptions which could be critical in space under conditions requiring reliable visual processing or if they contribute to sleep disturbances. It is unknown if there are any long-term pathologies associated with light flashes.

Two critical reviews by (Cekanaviciute et al., 2018) and (Kiffer et al., 2019) have summarized behavioral consequences as functions of charged particle type, energy, dose and time post exposure for space-relevant doses generally <25 cGy. They summarize how spatial, recognition, fear and social memory as well as anxiety and depression-like behaviors can be impaired in mice and rats of both sexes and evaluate the individual behavior tests. Similar dependencies are documented for inflammation, dendrite and synapse number reduction, neurotransmitter receptor changes, neuron loss and gliosis (microglia and astrocytes). They draw particular attention to the potential for overactive microglia to inappropriately destroy synapses and the relevance of higher abundance but lower LET particles such as helium ions versus less abundant but higher LET particles such as Fe ions. Most of these studies evaluated endpoints from 1 to 6 months post irradiation. (Patel et al., 2017) found that C57BL/6 male mice had significant deficits in recognition memory and reduced activity levels as well as increases in anxiety-like behavior that persisted as late as nine-months post-irradiation irrespective of the radiation type.

More sophisticated experiments bearing on cognitive performance have been performed on rats. (Rabin et al., 2009) have conducted many studies to quantify the negative effects of charged particles on memory and operant conditioning as functions of particle type, age at exposure, sex, and whole-body versus partial-body exposures showing that particles of all types could be deleterious and that body-only (head shielded) exposures led to substantial impairments implicating mechanisms involving circulating factors. (Marquette et al., 2003) showed that body-only gamma ray exposure to rats elicited proinflammatory cytokine production in the thalamus, hypothalamus, and hippocampus; vagotomy abrogated this response. The Rabin team also investigated nutritional countermeasures finding that dietary antioxidants found in blueberries and strawberries were shown to significantly ameliorate the disruptive effects of charged particles on memory and operant conditioning in rats (Rabin et al., 2009). (Britten et al., 2021) have developed methods for assessing executive function (attentional set shifting) as well as problem solving and cognitive flexibility in a touchscreen task (ARMIT) using rats of age corresponding to astronauts. Rats exposed to 10 cGy of helium or a simplified GCRsim exhibited significant deficits, and this was also seen in related studies with various ions. (Davis et al., 2016, 2014) developed a rat version of the human Psychomotor Vigilance Test (PVT) which quantifies impulsivity, reaction time and sustained attention in humans as well as in rodents as a translational model of cognitive function. They showed that 25 – 200 cGy of protons disrupted rodent PVT performance (decreased accuracy, elevated lapses in attention and slowed reaction times) over a 250-day testing period which correlated with levels of a dopamine transporter. A review by (Desai et al., 2022) evaluated space radiation studies in the context of, or in combination with, other spaceflight stressors such as isolation and confinement, altered gravity levels, closed environments, and especially sleep deprivation. These other stressors can contribute alone

or in combination with radiation to oxidative stress, inflammation, altered synaptic plasticity and altered neurotransmitter metabolism and involve multiple brain regions. The authors propose an investigation framework for future studies.

Structural changes to the brain have been observed by several investigators in terms of reductions in dendritic complexity, reduction in synapse number and type, reduction in expression of pre- and post-synaptic proteins, as well as partial demyelination of axons after low levels (~10 cGy) of charged particles (Carr et al., 2018; Dickstein et al., 2018; Parihar et al., 2020, 2015). The structural changes correlated strongly with cognitive impairment. In charged particle-irradiated mice, (Suman et al., 2013) found upregulation of Claudin, a protein associated with blood-brain barrier function along with impaired neurogenesis, increased oxidative stress, and deficits in spatial learning and memory.

Neuroinflammation and oxidative stress have been observed in many studies and informed by reduction in synapse number focused attention on microglia which normally regulate synapse number and are intimately involved in inflammation. (Paladini et al., 2021) and (Rienecker et al., 2021) addressed chronic microglia activation as a mechanism for radiation-induced neural and behavioral dysfunction and consequences of sexually dimorphic microglial phenotypes. They evaluated the ameliorating effects of temporary microglia depletion post irradiation using the orally-administered drugs PLX3397 & PLX5622. These are specific inhibitors of Colony-Stimulating Factor 1 Receptor (CSF-1R) which is a tyrosine kinase receptor expressed in the monocytic lineage of leukocytes. In the brain, CSF-1R signaling is essential for the migration, differentiation and survival of microglia. They demonstrated that PLX3397 or PLX5622 administration fully depleted microglia, which repopulated after drug administration was stopped, which allowed initial neuroinflammation to proceed but prevented a transition to chronic inflammation. This blocked radiation-induced impairment of object recognition memory, spatial memory, fear conditioning, active place avoidance and other behaviors in mice for periods up to 9 months. This was accompanied by a decreased neuroinflammatory status, reduced dendritic spine loss, altered microglia phenotype to normal homeostatic phenotype, and differential neuronal protein expression. Thus CSF-1R inhibition may be a promising countermeasure target.

Electrochemical signaling is the critical function of neural tissues and the process is conserved across species so that findings in rodents should be applicable to humans at the tissue level. In electrophysiology experiments with mouse organotypic dorsal hippocampal slice preparations, long-term potentiation (LTP), a tissue-level model of memory formation, was used to assess stimulation-induced synaptic strengthening and found hippocampus field-, dose-, and ion-specific modulation consistent with dysregulation of the balance between excitatory and inhibitory activity post-irradiation (Vlkolinský et al., 2008, 2007). Ventral hippocampus changes in network organization were also observed (Rudobeck et al., 2014). In longitudinal studies with iron ion exposure to male and female mice, (Miry et al., 2021) measured changes in hippocampal network functions (long term depression), neurogenesis and spatial memory that persisted for six months. But for the first time, they demonstrated the reversal of the impairments after 12 months which continued until 20 months post irradiation. Patch clamp studies were conducted on single neurons in C57Bl/6J mouse hippocampal slices after exposure to 10 or 100 cGy protons. At 90 days post-irradiation, changes included significantly hyperpolarized cell resting membrane potentials, decreased input resistance, upregulated persistent sodium current, and increased the rate of miniature excitatory post-synaptic currents, indicating a general reduction in pyramidal neuron excitability in the CA1 (Sokolova et al., 2015). These small alterations in passive membrane properties had a dramatic impact on network function in a computational model of the CA1 microcircuit, leading to a 50% decrease in rhythmic theta oscillation power. A study by (Klein et al., 2021) was one of the first to report responses of

the mouse brain to cosmic ray simulation mixed-ion fields with 5 or 6 components at total doses of 5 or 30 cGy. Unlike in single ion electrophysiology studies, the mixed-ion exposure did not alter intrinsic membrane properties of hippocampal CA1 neurons. However, inhibitory synaptic signaling was impaired and *in vivo* local field potential measurements in CA1 showed altered memory-associated hippocampal rhythms. Novel object recognition memory and water-maze spatial memory were impaired in the animals while anxiety measures showed no effect.

The totality of evidence from exposure of rodents to space-like radiation fields demonstrates the capability of space-like exposures to persistently alter brain structure, tissue-level function and behavior despite the lack of gross tissue changes and cell loss and predicts that similar changes may occur in humans. (Britten et al., 2021) have reviewed the recent CNS radiobiology literature and suggest that traditional radiobiological interpretations may not be appropriate for the chronic high LET exposures found in space. Instead, they suggest that cell killing- based models be replaced by loss-of-function models, that hippocampus-centric focus be expanded to multiple critical brain regions to explain cognitive impediments, and that neurons may not be the sole critical targets for neurocognitive impairment. The recent study by (Straume et al., 2025) takes the latter notion further and suggests from biophysical considerations that small membrane structures (e.g. synapses or mitochondria), rather than DNA, are the critical cellular/molecular targets for behavioral outcome measures. They further show that rather than dose, particle fluence independent of LET best fits the data.

While animal studies have largely addressed early and medium time-scale CNS changes that may pertain to in-mission performance, human studies with low dose chronic radiation exposure (excluding radiotherapy) have mostly addressed late neurodegenerative conditions. Recent epidemiology studies have been conducted on radiation clean-up workers, nuclear power workers, industrial radiographers, atomic bomb victims, submarine sailors, etc., to determine the incidence of late neurodegenerative conditions. The Million Person Study has recently detected a strong signal for elevated incidence of Parkinson's disease from a meta-analysis of 6 cohorts totaling over 500,000 persons (Dauer et al., 2024). The estimated excess relative risk (ERR) of death from Parkinson's was 0.17 per 100 mGy, a magnitude comparable to some cancer incidences. This finding confirms and extends that of (Azizova et al., 2020), who first reported elevated incidence in the 22,000-person Mayak worker study. Parkinson's disease is the second most common late neurodegenerative disorder after Alzheimer's disease, which does not exhibit the same radiation association. Parkinson's disease is associated with defects in dopaminergic neurons of the brain, especially in the substantia nigra and striatum. Like other neurodegenerative diseases there are dysfunctions in numerous cellular processes including protein homeostasis (leading to accumulation of aggregated proteins), mitochondrial function, calcium homeostasis, synaptic function, reactive oxygen processing, neuroinflammation, and aging (Antony et al., 2013; Wilson et al., 2023) most of which are also associated with radiation exposure to the brain (Blakely and Chang, 2007; Kempf et al., 2013). Rat and monkey studies with charged particle radiation confirm defects in monoamine neurotransmitter systems and behaviors associated with dopaminergic pathways (Belov et al., 2016; Belyaeva et al., 2017; Desai et al., 2022) suggesting that high LET radiations in space may be very effective in disrupting Parkinson's-associated cellular functions (Koike et al., 2005). There is also a vascular component to late neurodegenerative diseases and (Miller et al., 2022) reviewed studies focused on radiation effects on cerebrovascular function in both clinical and preclinical studies with animal models. They found that low to moderate radiation doses can lead to sex specific alterations in blood-brain barrier markers, cognition, as well as amyloid and tau levels, especially in transgenic mice expressing human amyloid precursor protein and mutant presenilin. Together, these findings suggest that at doses received

from high LET radiation in space, there could be an elevated risk of developing Parkinson's disease late in life and could be of greater magnitude than predicted by low LET exposures.

3.2 Risk of Cardiovascular Disease and Other Degenerative Tissue Effects

There is a well-documented link between high-dose radiation exposure and cardiovascular damage. Individuals who have received radiotherapy for primary cancers in the head, neck, or mediastinal regions exhibit a heightened risk of developing vascular and cardiac complications, including long-term radiation-induced heart disease. This association has been extensively reported in multiple studies and official reviews (NASA Human Research Program, 2022).

However, there is a significant knowledge gap regarding the direct impact of radiation on cardiovascular health, especially in long-duration space missions. While studies on low LET radiation have shown a clear association with cardiovascular risks in high-dose exposure contexts like cancer treatments (Little et al., 2023; Werneth and Huff, 2025), the effects of space radiation, particularly cosmic radiation, remain poorly understood. The risk of late-onset cardiovascular disease (CVD) in astronauts is concerning, but the exact threshold dose and cumulative effects of space radiation are still unknown, as those are still debated for non-astronauts (Kamiya et al., 2015; Wakeford, 2022, 2019). Mechanisms proposed for radiation-induced CVD include oxidative stress, inflammation, and mitochondrial dysfunction, which can damage cardiac function. For instance, Mair et al. (2024) highlighted how radiation exposure can reduce cardiac contractile force and increase arrhythmias, raising the risk of heart failure, while radiation-induced oxidative stress can impair mitochondrial DNA and normal cellular processes (Overbey et al., 2019).

In addition to radiation, spaceflight itself introduces factors that exacerbate cardiovascular risk. The absence of gravitational load in space leads to "aging-like" deconditioning, which manifests as arterial stiffening, insulin resistance, and a decline in physical fitness (Hughson et al., 2016). These effects, combined with radiation exposure, may compound CVD risks in astronauts, making it difficult to separate the effects of radiation from those of other spaceflight stressors.

The long-term cardiovascular health of astronauts has been a focal point of research, particularly given concerns about spaceflight-associated risks. A recent comprehensive study by (Charvat et al., 2022) compared NASA astronauts to a matched healthy Earth-based cohort, finding no significant excess in long-term CVD mortality risk among astronauts however there was evidence for increased morbidity. Assigning CVD risks to a spaceflight exposure is hindered by the small cohort size of the astronaut corps and the relatively low radiation exposures received by crews to date (Elgart, 2018).

Studies from European research groups have focused on low-dose, low-LET radiation exposures, particularly in environmental, clinical, and occupational settings. For example, the PROCARDIO project, which examined childhood cancer survivors, highlighted the need for further molecular epidemiological studies to better understand radiation-induced heart disease (Kreuzer et al., 2015). Meanwhile, NASA has focused on higher-LET radiation, such as heavy ions, which have been shown to induce more significant biological effects on cardiovascular health at lower doses compared to low-LET radiation. High-LET radiation can cause cardiac inflammation, DNA oxidation, and fibrosis at doses lower than those needed for low-LET radiation, suggesting that high-LET radiation has a heightened biological impact per unit dose (Boerma, 2015).

A major challenge in this research is the limitations of rodent models in replicating human CVD. Rodents, while useful in preliminary studies, have significant physiological differences from humans, leading to inconsistencies across studies. Efforts are being made to develop alternative models, such as rabbits, which share more similar cardiovascular systems with humans (Schlaak et al., 2020). Furthermore, mathematical modeling (Cucinotta et al., 2013a; Patel et al., 2016)is being employed to better extrapolate animal data to human risk, but these models still require refinement for more accurate predictions (Huff et al., 2022).

Assessing the cardiovascular risk of radiation exposure is further complicated by the multifactorial nature of CVD, which is influenced by factors such as genetics, blood pressure, and lipid profiles. Clinical risk prediction models (CPMs), widely used on Earth to assess these factors, could also be applied to astronauts to individualize risk assessments related to radiation exposure. By integrating personalized medicine into radiation risk models, NASA could enhance astronaut safety during long-term space missions and improve long-term health outcomes (Huff et al., 2022).

While substantial data exist on the effects of high-dose radiation (such as from cancer treatments), research on space radiation's specific effects on cardiovascular health is still limited. Although much of the current research focuses on low-LET, high-dose exposures in non-space contexts, these findings are important for understanding the potential risks posed by space radiation and guiding future studies.

3.3 Space Radiation Further Alters Microgravity-Induced Bone Health

As reviewed elsewhere, microgravity has dramatic effects on bone health (Grimm et al., 2016). Throughout life, bone resorption and new bone tissue formation are ongoing processes that help adaptation to changing loads. The absence of gravity and unloading of weight-bearing bones result in bone resorption, inducing a decrease in bone minerals, leading to osteoporosis and increased risk of renal stone formation due to the loss of calcium. While microgravity is the primary factor of bone health decrements in space, ionizing radiation can also damage bone (Grimm et al., 2016). Clinical radiation exposures have shown increased long-term risk of bone fractures due to the deterioration of bone quantity and quality (Willey et al., 2011). Studies with animal models have shown that exposure to radiation alone can also cause rapid bone loss and long-term suppression of bone formation (Bandstra et al., 2008). As reviewed by (Willey et al., 2011), space radiation alone can alter bone vasculature, damage osteoblasts and osteocytes, leading to a reduction in bone mineral density, and increase osteoclast number and activity, possibly contributing to osteoporosis. Various ground-based studies combining radiation and hindlimb unloading (HU) by tail traction have suggested cumulative adverse alterations to the bone structure that might worsen skeletal integrity caused by microgravity alone (Alwood et al., 2010; Kondo et al., 2010; Lloyd et al., 2012, 2012; Xu et al., 2014; Yumoto et al., 2010).

4. Radiation Effects on Organ Systems: Emerging Evidence

4.1 Exposure to Space Radiation Could Affect Immune Health

Despite its relevance, there is a notable lack of detailed data on how space radiation affects immune health. The NASA Human Research Program's (HRP) Immunology Evidence Report acknowledges radiation as a potential concern but largely focuses on stress and microgravity as dominant modulators of immune dysfunction, including viral reactivation (Satish and Crucian, 2022). Studies below LEO are limited, and most insights come from ground-based murine models simulating GCR and SPEs. These models suggest minor, transient reductions in immune cell populations – especially B cells, followed by CD8+ and CD4+ T cells and natural killer cells (Pecaut et al., 2006) – without reaching levels likely to cause clinically significant immunosuppression such as neutropenia. Nevertheless, radiation may modulate immune cell function and molecular signaling, and could interact with other stressors in space to affect immune resilience in complex, context-dependent ways.

Studies have confirmed that herpesviruses, including varicella-zoster virus (VZV), cytomegalovirus (CMV), Epstein-Barr virus (EBV), and herpes simplex virus (HSV-½), can reactivate in astronauts during and after spaceflight. (Cohrs et al., 2008) detected VZV DNA, antibodies, and infectious virus in astronaut saliva, demonstrating asymptomatic shedding, confirming the risk of reactivation during spaceflight. This suggests the potential for viral transmission among astronauts under spaceflight stress. (Mora et al., 2019)

found that 4% of viral sequences detected in ISS samples were derived from human herpesviruses, highlighting their persistence in the spaceflight environment.

Ionizing radiation and altered immunity contribute to herpesvirus reactivation. UV radiation and cosmic radiation can damage viral DNA and capsids, while microgravity may enhance aerosolization, prolonging viral stability and increasing transmission risk. Studies suggest that herpesviruses can persist on surfaces for hours, depending on humidity and temperature, with potential implications for infection control in enclosed spacecraft.

In alignment with spaceflight studies, a few recent ground-based studies have shown that both low LET (γ-rays, protons), high LET particles, and GCR can enhance viral reactivation in latently infected cells (Mehta et al., 2024). Notably, this reactivation can occur even in the absence of cytokines or the immune system involvement, indicating that the radiation effect is cell-intrinsic (Mehta et al., 2018). In murine models, ionizing radiation was shown to promote reactivation of latent polyomavirus (Shearer et al., 2005). Following irradiation, reactivation was more pronounced in certain mouse strains, suggesting that both immune status and genetic background influence susceptibility. However, the study also suggests that reactivation can occur even when cytokine activity is not significantly altered, which points to a more direct effect of radiation on latent virus reactivation.

Together with ongoing and upcoming NASA and external ISS studies, these investigations aim to comprehensively characterize immune responses during spaceflight, assess clinical risks for deep space missions, and support the development of targeted countermeasures and immune function biomarkers.

Part 3: Protective Strategies and Countermeasures Against Space Radiation

1. Current Solutions to Mitigate Space-Radiation Health Risks

1.1 Shielding Strategies and Transit Timing

NASA has adopted a multifaceted approach to managing radiation risks for the Mars mission. Potential habitat designs incorporate storm shelters for SPE protection (Simon et al., 2017), and mission schedules aim to minimize exposure during high solar activity (Gakis and Atri, 2022; Montesinos et al., 2021). Countermeasures to mitigate the harmful effects of space radiation can be broadly categorized into engineering-based solutions, conventional medical approaches, and emerging biotechnological strategies. Historically, engineering solutions such as passive shielding and mission design have been the primary focus of radiation protection (Durante, 2014). Passive shielding - using materials like polyethylene (Shavers et al., 2004) or hydrogen-rich compounds (Rojdev et al., 2009) - can reduce exposure to SPEs and GCR, but their effectiveness is limited by constraints, especially for deep-space missions beyond LEO (Durante and Cucinotta, 2011). Operational strategies, including storm shelters and timing extravehicular activities (EVAs) to avoid solar activity, are additional mission-level countermeasures (Norbury et al., 2019).

While shielding strategies offer some protection, data from NASA's Curiosity rover (Hassler et al., 2014; Zeitlin et al., 2013) show that astronauts receive the highest radiation dose during interplanetary transit, while exposure on the Martian surface is significantly lower, about one-third to one-half (Zeitlin et al., 2019), due to natural shielding. Although surface habitats can be enhanced with regolith, shielding options during transit are limited, making reduced travel time a critical factor in lowering overall radiation risk.

2. Future Countermeasures for Long-Duration Missions

Since 1968, NASA has been actively researching radioprotective drugs and antioxidants as pharmacological countermeasures such as radioprotective drugs and antioxidants to prevent or mitigate radiation-induced cellular damage and safeguard astronauts (Smith and Thomson, 1968). This experimental approach was improved by utilizing simulated GCR (GCRsim) at NSRL, facilitating researchers in studying the effects of deep-space irradiation and countermeasures on biological samples and more

complex *in vivo* models (Huff et al., 2023; Norbury et al., 2019). One promising candidate is metformin, a well-known prescribed drug for Diabetes Mellitus Type II, which has demonstrated radioprotective capabilities in human fibroblasts as well as irradiated mice (Siteni et al., 2024). While not yet approved or used in spaceflight, this drug has sparked widespread interest as a potential prime candidate for pharmacologic alteration of the space radiation risk.

2.1 Terrestrial FDA Approved Therapeutics for Acute Radiation Syndrome: A Viable Shield?

To date, no radiation-specific medical countermeasures are in routine use by astronauts. However, the current therapeutic radiation countermeasures employed for astronauts are largely adapted from terrestrial medicine. The U.S. Food and Drug Administration (FDA) has approved three medical interventions for ARS based on terrestrial applications. These include First, Filgastrim (Neupogen®), Pegfilgastrim (Neulasta®), and Sargramostim (Leukine®), which stimulate white blood cell production and recovery following radiation-induced bone marrow suppression (Lazarus et al., 2022). While these agents are effective in managing short-term hematopoietic effects of high-dose radiation on Earth, they have not yet been implemented in spaceflight and are not targeted to mitigate long-term health consequences following radiation exposure; indeed, some evidence suggests they could potentially increase cancer risk (Carnell, 2021).

2.2 Potential Therapeutic Interventions Targeting Mitochondrial Dysfunction in Spaceflight

Spaceflight-induced mitochondrial dysfunction may result from increased oxidative stress, HIF-1α activation, and downregulation of oxidative phosphorylation (OXPHOS), potentially compromising cellular energy production, tissue integrity, and immune function (da Silveira et al., 2020). Addressing these challenges could involve a range of therapeutic strategies targeting mitochondrial calcium homeostasis, inflammation, ROS production, and OXPHOS function.

One potential approach includes antioxidants such as superoxide dismutase mimetics (e.g., MnTBAP, EUK8) and mitochondrial permeability transition pore inhibitors (e.g., NIM811), which could help mitigate oxidative stress and restore mitochondrial function. In addition, compounds that promote mitochondrial biogenesis, such as kaempferol, epicatechin, or bezafibrate, may offer therapeutic benefits by enhancing mitochondrial health. Furthermore, strategies aimed at preventing mitochondrial calcium dysregulation (e.g., MCU inhibitors) and inhibiting the release of mitochondrial danger-associated molecular patterns (mtDAMPs) could help address some spaceflight-related mitochondrial dysfunction. Finally, antagomir treatments targeting microRNAs (e.g., miR-16-5p, miR-125b-5p, let-7a-5p) have been shown to reduce inflammation, DNA double-strand breaks, and mitochondrial dysfunction in 3D microvessel cell cultures exposed to simulated deep-space radiation (0.5 Gy GCR) (McDonald et al., 2024), however, such approaches are experimental in nature and not available for human treatment.

Depletion of essential vitamins and cofactors during space missions may further exacerbate mitochondrial damage. Supplementing with vitamins B1, B2, B3, folic acid, and cofactors such as α-lipoic acid, coenzyme Q10, and L-carnitine might support mitochondrial function and potentially reduce oxidative damage. These could also help mitigate risks of muscle atrophy, immune dysregulation, and impaired tissue repair during space missions (Crucian et al., 2013; Garrett-Bakelman et al., 2019; Smith et al., 2015).

Among the potential candidates, kaempferol (KMP) appears promising, as it possesses antioxidant and HIF-1α inhibitory properties and could stimulate mitochondrial biogenesis via PGC1α activation (Mylonis et al., 2010; Wang et al., 2018). In rodent models, KMP has been shown to alleviate radiation-induced liver damage, preserving organoid function and preventing significant tissue loss after exposure to simulated galactic cosmic radiation (GCR) (Guarnieri et al., 2025). Due to its safety profile and potential efficacy, KMP could be a leading candidate for counteracting mitochondrial dysfunction during space missions.

Mitochondrial impairment during spaceflight has been associated with clinically relevant outcomes such as cardiovascular deconditioning, neurodegeneration, musculoskeletal decline, and immune system suppression. While the above therapeutic approaches show potential, further studies are needed to assess their long-term effectiveness and feasibility in the context of spaceflight. Nevertheless, these strategies could offer valuable countermeasures to mitigate spaceflight-induced mitochondrial damage, supporting astronaut health and recovery after missions.

3. Gene-Editing Technologies: The Next Generation Therapeutics

3.1 The Face of Gene-Editing Technology

Future deep space missions are expected to expose crews to significantly higher levels of ionizing radiation compared to previous missions aboard the ISS or short-term Lunar missions. While a 6 to 12-month stay on the ISS typically results in doses between 30 and 120 mGy, projected missions to Mars are estimated to result in exposures four to ten times greater (Norbury et al., 2016; Simonsen et al., 2020). Traditional countermeasures against space hazards, such as radiation and gravity changes, either offer only partial protection or are currently insufficient for the extended time frames required for long-duration (Moon, Mars) missions. Given these limitations, innovative strategies, including gene editing technologies, are being considered to ensure human survival (Szocik et al., 2021). However, the potential use of gene editing in space exploration introduces profound ethical dilemmas (Reed and Antonsen, 2018) for astronauts and their potential offspring, raising generational concerns about the long-term effects of such modifications, especially if introduced as germline editing.

The CRISPR-Cas9 gene-editing system, discovered in 2014 by Jennifer Doudna and Emmanuelle Charpentier, has revolutionized genetic engineering, leading to rapid advancements in the field (Doudna and Charpentier, 2014). While early versions of the CRISPR system exhibited significant off-target activity (Zhang et al., 2015) and risks of unintended genetic alterations such as deletions and genomic rearrangements, resulting in gene silencing and potentially fatal neoplastic outcomes (Guilinger et al., 2014), subsequent improvements including base editing and prime editing (Antoniou et al., 2021; Newby and Liu, 2021; Testa and Musunuru, 2023), have offered more precise and safety tools for gene modification. These advancements allow for targeted gene corrections, avoidance of double-stranded DNA breaks and therefore, offer promising therapeutic potential for various genetic disorders, as demonstrated in numerous preclinical animal studies (Choi et al., 2022; Reichart et al., 2023; Suh et al., 2020). Some of these techniques are already progressing through clinical trials (U.S. Food and Drug Administration (FDA), 2023), underscoring their potential for future applications, including space travel.

In light of these threats, gene editing technologies have been discussed as potential countermeasures (Cortese et al., 2018; Szocik et al., 2021). These tools could be used to enhance astronaut resilience, offering the possibility of altering genetic responses to radiation and microgravity. For example, gene editing might be employed to improve DNA repair mechanisms, boost cellular resilience, or protect against radiation-induced damage. However, the ability to directly modify human DNA raises profound ethical concerns. One key issue is the potential for unintended consequences, including the alteration of traits that could affect not only the individual astronaut but also their descendants. The ethical implications of altering the human genome for space travel thus extend beyond individual health and well-being to include the potential for generational impacts, which raises the question of whether it is ethical to make permanent changes to the human genome without fully understanding the long-term effects. In addition to the morale implications, there are practical and financial barriers to the widespread use of gene editing. Current genome-editing therapies, such as those for sickle cell disease, cost more than $2 million per patient (Policy and Global Affairs and National Academies of Sciences, Engineering, and Medicine, 2023). The high costs associated with these treatments would likely be even greater in the context of space exploration. This financial burden may limit access to these technologies, potentially

creating inequalities in space exploration and raising concerns about the fairness and accessibility of genetic enhancements. As space exploration advances, it will be essential to carefully weigh the benefits and risks of gene editing technologies. While they hold promise for addressing the challenges of long-duration missions, including those to Mars, the ethical implications - particularly in terms of generational health - must be carefully considered. Ensuring these technologies are used responsibly and equitably will be key to navigating the complex future of space exploration and human adaptation to extraterrestrial environments.

3.2 The Power of Genetic and Epigenetic Editing

Among the emerging radiation mitigation strategies could be somatic cell gene and epigenetic editing (SoCGEE). These approaches hold transformative potential for mitigating radiation-induced damage and other spaceflight-associated stressors. While gene and epigenetic editing can be applied to either somatic or germline cells, each approach entails distinct, technical, and biological considerations (Ormond et al., 2019; Rossant, 2018). To date, NASA has not funded gene editing research specifically for space radiation countermeasures, though this area holds promise for future applications. Ethical considerations, technical challenges and the potential for unintended side effects, such as off-target mutations (Tsai and Joung, 2016) and increased cancer risk remain significant (Kendal, 2024; Szocik et al., 2020). As deep-space exploration transitions from concept to reality, the development of long-term, robust countermeasures such as SoCGEE may become critical for safeguarding the health and performance of astronauts.

3.3 Radioprotective Gene Candidates

Some specific genes have emerged as potential therapeutic targets for radioprotection with the potential to offer targeted and long-lasting solutions to the risks posed by space radiation. Previous studies have explored the delivery of genes that encode antioxidant enzymes, such as superoxide dismutase (SOD2 or MnSOD), catalase, interleukin (IL-3), hepatocyte growth factor (HGF), fibroblast growth factor 2 (FGF2), vascular endothelial factor (VEGF), and aquaporin 1 (AQP1) to reduce oxidative stress caused by radiation. Such genes have been demonstrated to protect cells and tissues from radiation damage in experimental animal models (Everett and Curiel, 2015). Cells expressing MnSOD demonstrated resistance to radiation-induced damage (Southgate et al., 2006). This was attributed to the enzyme's ability to reduce oxidative stress and protect cellular components, such as DNA and proteins, from reactive oxygen species (ROS). Similarly, animal models treated with MnSOD gene therapy approaches demonstrated improved survival rates and less radiation-induced damage compared to controls (Southgate et al., 2006). Previous studies have focused on mitochondria as a key site of radiation-induced oxidative damage. Radiation generates ROS within mitochondria, leading to cell damage and apoptosis. To address this, the catalase enzyme, which breaks down hydrogen peroxide into water and oxygen, was targeted to mitochondria using a mitochondrial-targeting sequence. This ensured localized reduction of ROS in the organelle most affected by radiation. The catalase gene was delivered to cells via plasmid DNA encapsulated in liposomes. Transfected cells expressing the transgene showed significantly higher survival rates and lower ROS levels following radiation exposure compared to control groups (Epperly et al., 2009). In experimental models, liposome-delivered catalase gene therapy provided radioprotection to radiation-sensitive tissues, such as those in the hematopoietic and gastrointestinal systems. Treated animals exhibited improved survival rates and reduced radiation-induced tissue damage (Epperly et al., 2009). The transgene's ability to reduce ROS at its source was identified as the key mechanism underlying the enhanced radioprotection. Additionally, this mitochondrial-targeted antioxidant strategy also reduced markers of oxidative stress and DNA damage in both treated cells and tissues. In addition, targeting hematopoietic cells via overexpression of granulocyte colony-stimulating factors demonstrated protective effects against bone marrow depletion caused by radiation exposure in animal models (Li et al., 2015).

Overall, the discussed experimental approaches have demonstrated to improve the recovery post radiation exposure and mitigate the risks associated with accidental or occupational radiation exposure. However, the long-term safety and efficacy of these techniques have not been fully evaluated, indicating the need for further preclinical and clinical studies. While most of the experimental studies focused on acute radiation exposure, future research should explore its efficacy in models of chronic radiation exposure, mimicking future manned missions with long-duration radiation exposure.

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