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RAD SEN REGEN A Translational Framework for Regenerative Resilience in Human Spaceflight

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Perspective

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Abstract

Human spaceflight creates a biological stress continuum extending from mission preparation through launch, altered gravity, radiation, extravehicular activity and postflight recovery. RAD-SEN-REGEN proposes regenerative resilience as a translational framework linking DNA damage, cellular senescence, mitochondrial dysfunction, inflammatory signaling and regenerative capacity. It positions characterized mesenchymal stromal cells, MUSE cells and extracellular vesicles as research platforms for investigation while distinguishing material quality, oncologic vigilance and recovery science from premature therapeutic claims.

Introduction

Human exploration beyond Earth exposes the body to a combination of altered gravity, ionizing radiation, confinement, circadian disruption, operational workload and environmental constraints. Integrated omics investigations have demonstrated that these exposures affect mitochondrial regulation, immune function, vascular biology, musculoskeletal integrity, genome stability and cellular aging [1–3]. Microgravity also modifies stem-cell proliferation, lineage commitment, mechanotransduction and stress responses, while radiation can induce DNA lesions and senescent phenotypes that differ from those produced by conventional terrestrial irradiation [4–7].

These discoveries have transformed the resolution with which space medicine can describe biological disruption. Nevertheless, description is not restoration. An astronaut may complete training, tolerate flight and extravehicular activity, return to Earth and regain functional performance without the exposure having been biologically neutral. Molecular injury, altered inflammatory signaling, mitochondrial stress and loss of regenerative reserve may persist beneath the threshold of an immediately visible clinical lesion [1–3, 8].

RAD-SEN-REGEN addresses this translational gap. It proposes that regenerative resilience should be studied across the entire exposure continuum and that the quality of the biological material used to investigate or ultimately modulate recovery is integral to the science. The framework does not advocate premature clinical use in astronauts. It establishes a route by which evidence from radiation biology, senescence research, clinical-grade cell manufacturing, oncology and aging biology can be organized into testable, human-relevant space-health research.

Theoretical framework

Regenerative resilience as a biological property

Operational resilience is commonly inferred from the ability to maintain performance or recover function. Regenerative resilience is a different construct: the capacity of cells, tissues and regulatory systems to preserve identity, repair damage, control inflammatory signaling and restore homeostasis after exposure.

It includes DNA-repair competence, mitochondrial reserve, redox balance, immune coordination, progenitor-cell fitness and the avoidance of persistent senescence-associated secretory signaling.

Cellular senescence is particularly relevant because it is simultaneously protective and harmful. Stable cell-cycle arrest can prevent the propagation of damaged genomes, yet accumulation of senescent cells and their secretory phenotype can amplify inflammation, alter tissue niches and impair repair. Spaceflight-associated radiation and microgravity can influence p16INK4a, p21, SA-β-gal activity, γH2AX, 53BP1, NF-κB signaling and mitochondrial function [4–8]. These are not merely experimental endpoints; together they describe whether exposed biology retains the capacity to recover.

The exposure continuum

Biological exposure begins before launch. Mission-dependent preparation may include intensive conditioning, centrifuge loading, hypobaric or hyperbaric training, neutral-buoyancy operations, sleep disruption and emergency simulations. These activities are not biologically equivalent and should not be collapsed into a single claim of hypoxia or barotrauma. Each creates a distinct physiological demand that interacts with baseline metabolic, inflammatory and regenerative reserve. Flight, extravehicular activity and readaptation to terrestrial gravity then add further layers of stress, as summarized in Fig. 1.

Translational regenerative systems

Characterization is not a regulatory afterthought

‘Stem cells’ cannot be treated as a uniform intervention or experimental reagent. Tissue source, donor selection, isolation, passage, cumulative population doubling, culture medium, cryopreservation, viability, phenotype, potency and release criteria alter biological behavior. Research-grade cells may be appropriate for discovery experiments but are not automatically suitable for administration. Conversely, material produced under clinical or GMP-oriented controls is not automatically approved or effective for a particular indication. Translational space medicine must preserve this distinction.

The minimal phenotypic criteria proposed by the International Society for Cell & Gene Therapy remain a foundational reference for MSC identity, but contemporary translation additionally requires assays connected to the intended mechanism of action [9]. For space-health applications, identity, purity, potency, genomic stability, sterility, endotoxin, mycoplasma, traceability, chain of custody, stability and lot consistency should be incorporated as experimental variables.

Wharton’s jelly-derived mesenchymal stromal cells

Wharton’s jelly-derived MSCs provide a perinatal, ethically accessible and biologically young source with proliferative and immunomodulatory properties. Their relevance does not arise from source alone.

Prolonged in-vitro expansion may promote replicative senescence, phenotypic drift, altered secretory profiles and loss of potency; passage and population doubling therefore matter when comparing published studies or designing translational products [10, 11].

The feasibility of generating extensively characterized material is illustrated by a 2026 Mexican quality-control certificate for lot RL-F0326, originating from placental/umbilical-cord tissue. Flow cytometry reported viability of 97.43%; CD44, CD73 and CD105 expression of 100%; CD90 expression of 99.75%; and 0% reported expression for CD34, CD45, HLA-DR, CD14, CD11b and CD19. The same batch documentation reported negative mycoplasma testing, endotoxin of 0.01 EU/mL, and bacterial, fungal and yeast counts below 1 CFU/mL, together with donor serology and adipogenic, osteogenic and chondrogenic differentiation images. A karyotype image and an oncogenicity panel were included, although absence of a complete interpretive report precludes using those images alone as proof of genomic normality or absence of oncogenic risk. These data are presented as an example of existing manufacturing documentation, not as independent efficacy evidence or authorization for a spaceflight indication.

MUSE cells and stress-enduring phenotypes

Multilineage-differentiating stress-enduring (MUSE) cells were originally identified as an SSEA-3-positive population within mesenchymal tissues and cultures [12]. Published work describes enhanced tolerance to genotoxic and oxidative stress and differences in DNA-repair dynamics relative to non-MUSE MSC populations [13, 14]. These properties make MUSE cells relevant to the concept of regenerative resilience. However, SSEA-3 expression alone is not a complete release strategy; enrichment, purity, identity, genomic stability and functional stress-response assays remain necessary.

Cell-free systems

Extracellular vesicles may ultimately be operationally attractive where viable-cell storage, culture recovery or containment is impractical. Their characterization must be equally rigorous. Source-cell state, collection conditions, isolation, particle identity, purity, cargo, dose, sterility, storage stability and potency determine interpretability. The generic term ‘exosomes’ should be reserved for preparations meeting accepted biogenesis and characterization criteria; otherwise, ‘extracellular vesicles’ is more accurate [15, 16].

Discussion

The central proposition of RAD-SEN-REGEN is that human spaceflight should be understood not only as an exposure to be survived but as a sequence of biological transitions requiring preservation and recovery of regenerative capacity. This reframing connects established physiological countermeasures with a molecular and cellular layer that remains comparatively immature. Exercise, shielding, nutrition,

habitat engineering and pharmacology remain essential; regenerative systems would complement them by addressing mechanisms that may persist after performance has recovered.

A second contribution is the insistence that translational quality cannot be separated from biological interpretation. Discordant findings across MSC studies may reflect not only platform differences but also tissue source, donor, passage, culture, cryopreservation, viability and potency. The use of poorly defined material can make a negative experiment uninterpretable and a positive experiment irreproducible. Human-relevant space biology therefore requires traceable materials and assays connected to clinically meaningful functions.

Oncology and aging biology provide a mechanistic bridge but must not be treated as equivalents of spaceflight. DNA damage, oxidative stress, mitochondrial dysfunction, senescence-associated signaling, immune dysregulation and altered tissue niches occur across these fields. Their intersection can inform monitoring and risk assessment, including the possibility that trophic or immunomodulatory signals may be contextually undesirable in tissues with premalignant or malignant susceptibility. Regenerative strategies must therefore include oncologic vigilance, genomic-stability assessment and long-term follow-up rather than assume that anti-inflammatory activity is universally beneficial.

The framework also supports reducing unnecessary animal experimentation by prioritizing human-relevant systems such as organoids, tissue models, clinically characterized cellular products and multi-omic monitoring where scientifically appropriate. It does not imply that all animal models can immediately be discarded. Model selection should be driven by the biological question, predictive validity and the principles of replacement, reduction and refinement.

RAD-SEN-REGEN translational pathway

Translation should proceed sequentially: evidence synthesis and material qualification; terrestrial human-cell and organoid validation; analogue and radiation studies using matched controls and recovery intervals; flight-compatible stability and hardware testing; and only then, if justified, regulated human investigation. At every stage, predefined safety thresholds and mechanistic endpoints should prevent technological enthusiasm from outrunning evidence.

Conclusion

Space medicine has reached a point at which documenting damage is necessary but insufficient. RAD-SEN-REGEN proposes regenerative resilience as a unifying translational objective linking biological readiness, protection during exposure and postflight restoration. Low-passage WJ-MSCs, MUSE cells and rigorously characterized extracellular-vesicle systems provide candidate human-relevant platforms for this research, but their value depends on precise identity, manufacturing quality, potency and risk assessment. The future of human spaceflight biology should not be measured only by how much deterioration the body can tolerate. It should also be measured by how responsibly science learns to preserve and restore the biological capacity to recover.

Declarations

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Figures

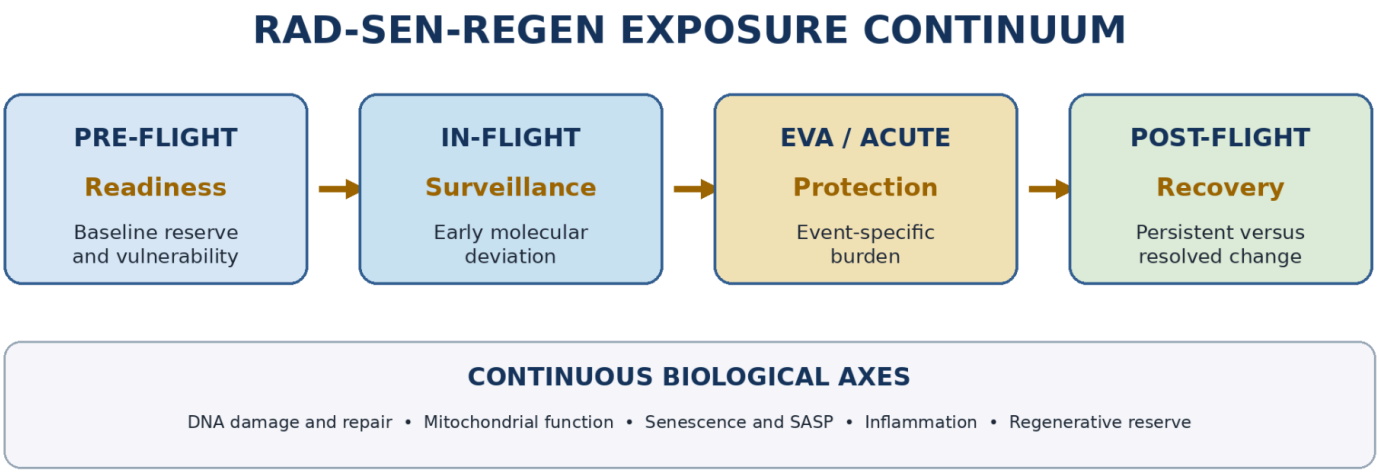


Figure 1

RAD-SEN-REGEN organizes readiness, surveillance, protection and recovery across the human-spaceflight exposure continuum.