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STEM CELLS: POLICIES FROM THE BENCH TO THE CLINIC (G MOLL AND N DRZENIEK, SECTION EDITORS)

MSCs in Space: Mesenchymal Stromal Cell Therapeutics as Enabling Technology for Long-Distance Manned Space Travel

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Abstract

Purpose of Review Advancements in space travel, such as space tourism into Earth's orbit, but also the prospect of long-distance manned space travel to other celestial bodies such as Mars, has generated a clinical need for new enabling technologies to support the long-term well-being of humans during their passage. Here, we will give an outline on the clinical need and practical considerations to MSC therapy as enabling technology for long-distance manned space travel.

Recent Findings Long-distance space travel entails a threat to the health of astronaut crews due to the low gravity environment and exposure to toxic radiation in space. Multi-organ-system degenerative changes, such as decline in musculoskeletal, hematopoietic, immune system function, and in particular risk of genetic mutations and cancer, are major health concerns. Physical training, pharmacological agents, and protective shielding are among the currently available methods to counteract harmful effects. However, a potential lack of adequate shielding, side effects of pharmacological compounds, and limitations to physical training suggest a need for new countermeasures, to protect space travellers to the best extent. Here, the prospect of cell-based therapy, e.g. mesenchymal stromal/stem cells (MSCs), has been subject to intense research, due to their potent regenerative and immunomodulatory properties. Off-the-shelf MSC therapeutics can be easily maintained in space due to the ambient extremely low-temperature environment, and cryorecovery and even culturing of MSCs under microgravity were shown to be feasible.

Summary Designing new therapy against harmful radiation is urgent need in space travel. Here we will discuss aspects related to clinical MSC administration to optimize their therapeutic benefit. MSC-based therapy may aid in evolving protective countermeasures for space travellers.

Keywords Cosmic radiation–induced tissue damage · Space disease/sickness · Mesenchymal stromal/stem cells (MSCs) · Regeneration and immunomodulation · Therapeutic cell delivery and dosing · Cryopreservation and cryostorage · Freeze-thawing · Innate and adaptive immune responses

Abbreviations

GCRs	Galactic cosmic rays
HZE ions	High-energy nuclei component of GCRs with an electric charge greater than + 2
ISS	International Space Station
LEO	Lower Earth orbit

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LET	Linear energy transfer (high LET radiation from neutrons and heavily charged particles)
SPEs	Solar particle events
TPs	Electrons and protons in the Van Allen Belts
CNSA	China's National Space Administration
NASA	National Aeronautics and Space Administration (of America)
UAESA	United Arab Emirates Space Agency
TRL	Technology Readiness Level

Introduction

The year 2021 marks several major breakthroughs in space travel, with an acceleration in efforts of government agencies, corporate/private enterprises, and private–public partnerships, to put humans into space, both in the prospect of interplanetary long-distance travel and in space tourism in Earth's closer proximity. This acceleration in manned space flight calls for increased efforts to develop novel adjunct medical technology to support the well-being of space travellers [1]. In this perspective, we will give an outline on the clinical need and practical implications for the use of regenerative and immunomodulatory therapeutic mesenchymal stromal/stem cells (MSCs) [2•, 3•, 4–7], to antagonize any detrimental health-risks associated with long-term space travel [1, 8, 9, 10••, 11], such as musculoskeletal wasting, hematopoietic and immune system compromise, and multimorbid toxicity resulting from prolonged exposure to space radiation and confined low-gravity environment.

Human space exploration has been going on for more than 70 years since the early American and Russian space programs have started in the 1950s [12]. The years 2020–2021 have brought notable acceleration in both government and private efforts. Key interplanetary government efforts entail landing of the Chinese Mars rover 'Zhurong' in April 2021 as part of the 'Tianwen-1' mission organized by China's National Space Administration (CNSA), to send a robotic space craft to Mars. This was following suit to landing of the American Mars rovers 'Curiosity' in Gale Crater on August 6, 2012, and 'Perseverance' in Jezero crater on February 16, 2020, as part of the 'Mars 2020 mission' of the National Aeronautics and Space Administration's (NASA) Mars exploration program. The Mars Mission 'Hope' of the United Arab Emirates Space Agency (UAESA), that has reached Mars on February 9, 2021, is another notable effort to Mars exploration.

Interestingly, multiple corporate and private efforts, as well as private public partnerships, have also stepped on the stage and rapidly progressed lately, culminating in the 'Billionaire Space Race' that cemented the feasibility of 'Space Tourism' in July 2021 [13–15]. This is exemplified by the two crewed near-Earth space hops of Richard Branson on July 11, 2021 (Virgin Galactic – SpaceShipTwo rocket, peak altitude 88 km) and Jeff Bezos on July 20, 2021 (Blue Origin – New Shepard rocket, peak altitude 107 km, thus passing the Karman line of 100 km). Importantly, this was recently followed by the first successful launch of an all-civilian crew by entrepreneur Elon Musk and team on September 16, 2021 (Space X – 'Inspiration-4' mission with the SpaceX Crew Dragon flying at 575 km, which is 160 km higher than the orbit of the International Space Station; ISS) sending for the first time four exclusively private citizens on a 3-day mission into Earths' orbit — circling Earth three times before reentry of their craft [16, 17].

Akin to national and transnational efforts to explore Mars, many of the corporate/private programs see manned long-distance travel to Mars as a first major step-stone to interplanetary colonialization. As shown by the extended duration space missions on Earth orbiting space stations, such as the 'American Astronaut Twin Studies' conducted on the International Space Station (ISS) [9, 10••, 11], a major drawback to manned exploration/long-distance travel are the considerable health challenges posed on space travellers [1]. The high-altitude environment is very challenging to astronauts, since microgravity triggers musculoskeletal atrophy, remote and restricted habitability causes great psychological stress, and most importantly, the exposure to space radiation significantly endangers the health and long-term well-being of astronauts [1, 18]. In ISS orbit, major sources of ionization radiation are composed of three primary sources: (i) galactic cosmic rays (GCRs), (ii) solar particle events (SPEs), and (iii) electrons and protons in the Van Allen Belts (TPs) outside the spacecraft. Considering interplanetary travel, particularly, the highly charged GCRs create a hostile environment outside the lower Earth orbit (LEO) [19], which can promote long-term development of degenerative tissue defects, such as cardiovascular changes, genetic mutations, and cancer [1, 20].

During interplanetary space travel, the protection of astronauts from SPE storms is a great challenge. During missions to Mars, there is high risk for astronauts to be exposed to SPE radiation events, which can be harmful to space systems and crews alike [21], thus impacting on mission planning, timelines, and operational decisions. However, researchers are constantly advancing genomic, proteomic, and metabolomic techniques, to improve the detection of any harmful effects from space radiation on human physiology [1, 11]. In contrast, developing medical countermeasures to actually mitigate or treat radiation injury is an urgent medical need for the astronauts on extended missions. There exist at least two approaches to counteract radiation injury in space. First of all, shielding is an effective method against SPEs, but it often fails to protect the crew from the biological effects of fast moving and highly-charged GCRs [22]. In addition, the administration of pharmacological agents is another method of radiation protection, but radioprotective pharmacological

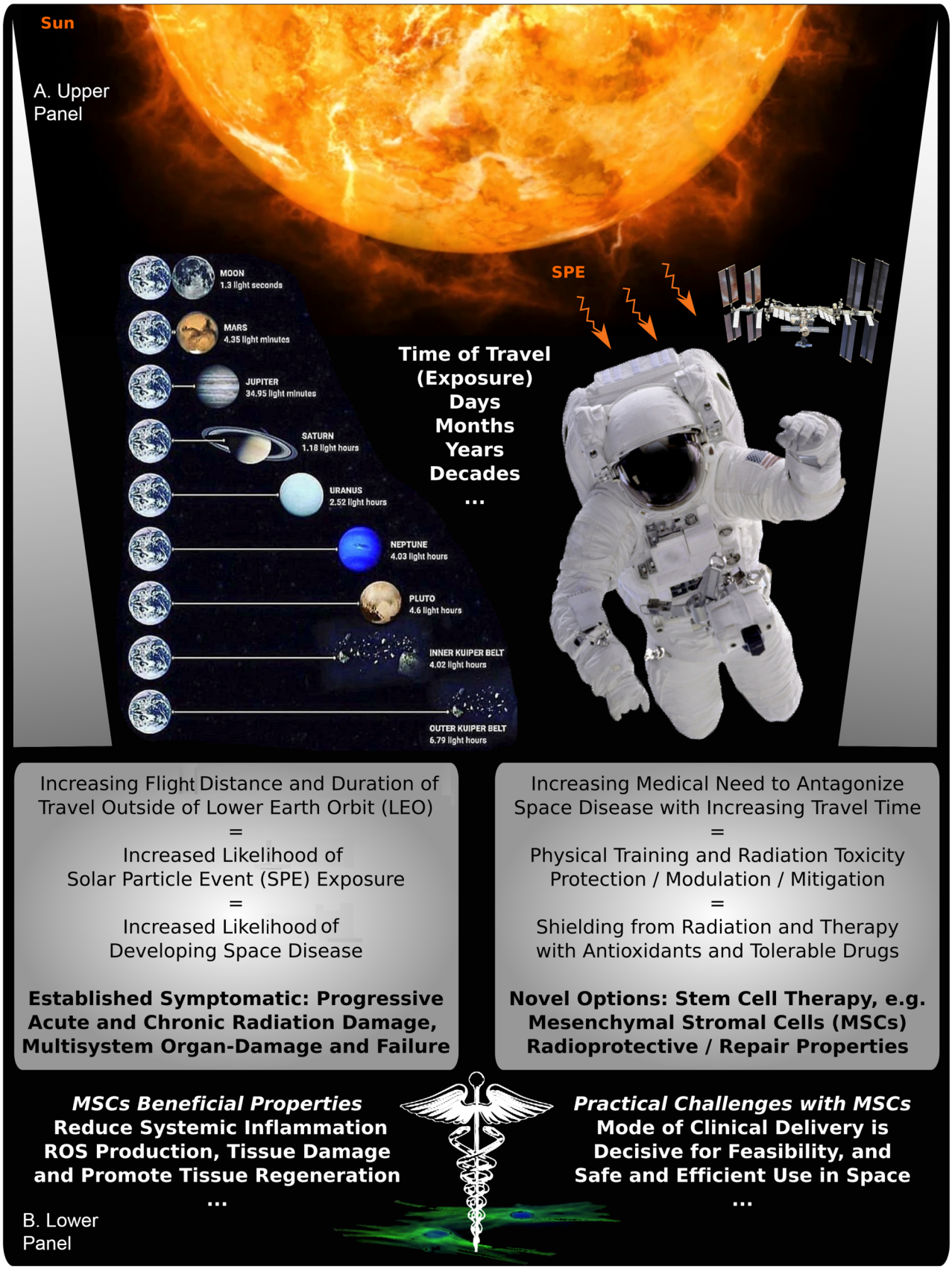
compounds have considerable side effects (e.g. decreased renal perfusion and angioedema) and are therefore difficult to use in astronauts exposed to space radiation [23]. This encourages a continuous search for more amenable and tolerable drugs to ameliorate the effects radiation exposure.

Stem cells therapy is a promising field in regenerative medicine, which has greatly advanced recently [2•, 24–26]. The field has now reached a technological readiness level (TRL) [27, 28] that robustly supports operability in Earth environments with its supportive infrastructure. The TRL is a measure developed by NASA for assessment of technological readiness on a scale from 1 to 9, spanning different phases, e.g. 1 Basic technology research, 2 Research to Prove Feasibility, 3 Technology Development, 4 Technology Demonstration, 5 System/Subsystem Development, and 6 System Test, Launch and Operations. However, the implementation of stem cell therapy in space entails particular logistic challenges, such as high cargo costs, suitable storage methods, and considerable practical limitations related to actual clinical cell application/delivery to patients [2•, 3•, 4–7]. While hematopoietic stem cell transplantation (HSCT; e.g. to recover a dysfunctional hematopoitic system) is already a well-established entity with > 50.000 annual procedures globally [24, 29–31], MSC therapy has only been developed more recently, aiming to provide novel regenerative and immunomodulatory treatments for great range of clinical indications [3•, 7, 24, 26, 32, 33].

MSCs are multipotent progenitor cells with limited self-renewal capacity [25, 34] that can be derived from several tissue sources (e.g. bone marrow, adipose tissue, and perinatal tissues, abbreviated BM, AT, and PT, respectively), which may entail variations in their safety and efficacy profile [2•, 5]. According to the International Society for Cell and Gene Therapy (ISCT) [35], the minimal criteria for defining MSCs are (i) plastic adherent fibroblast-like morphology, (ii) presence/absence of a panel of defined cell surface markers, and (iii) multilineage differentiation potential. More updated criteria have also been proposed recently [2•, 5, 36, 37]. Preliminary studies aboard ISS have demonstrated that MSCs can be retrieved from cryostorage and expand in microgravity with maintenance of 'stemness' [38], thus supporting MSCs' therapeutic application in space. However, a major limitation in the use of MSCs as an immediate therapeutic in space is the current lack of understanding considering the best modality of clinical MSC application to patients for optimal therapeutic benefit [2•, 3•, 4–6]. In this review, we will first introduce how cosmic radiation and the altered physical environment (e.g. microgravity) affect the physical health of astronauts, which will then be followed by an outline on MSC mediated prevention of radiation injury. Finally, we will discuss optimal modes of MSC delivery to achieve the optimal therapeutic outcome.

Radiation Exposure Causes Multisystem Organ Failure

Interplanetary travel to Mars and beyond entails flight schedules lasting several months (Fig. 1A), which has been linked to 30 different health risks within NASA's Human Research Program [1]. The risks ranked as 'red' have the highest priority based on both the likelihood of occurrence and the severity of their impact on human health, performance in mission, and long-term quality of life. During this passage, the combination of GCRs and protons released during SPE's contributes to the most prevalent harmful components of radiation outside of the LEO. Although SPE's overall impact on human health during interplanetary transit is not clear today, first clinical studies have studied the dose distribution regarding whole body irradiation. Importantly, compared to internal organs, the directly exposed skin is more susceptible to absorb the low energy spectra of protons and nuclei; hence, SPE dose is higher for skin than internal organs and may promote skin injury and cancer [39]. However, it is clear that the health challenges during prolonged space travel are multifactorial, thus leading to progressive multisystem organ failure in relation to the time of travel and the dose or harmful radiation that has been accumulated during the flight (space exposome) [1]. In particular, due to the combined effect of SPE radiation and prolonged living inside artificial microgravity, crew members often experience serious health problems like skin injury, haematological changes, and immune system suppression, followed by development of degenerative vascular changes, and elevated risk for genetic mutations and cancer [20]. The high linear energy transfer (LET) radiation in the GCR spectrum damages biomolecules (e.g. deoxyribonucleic acid (DNA), proteins, and lipids) and can also alter the organelles and cellular structure. Furthermore, aging associated degenerative tissue changes, such as myocardial remodelling and fibrosis, can be developed due to the radiation-induced increase in oxidative stress [40]. Recently, the NASA 'Astronaut Twin Study' has been performed to study biological responses of the human body during a year-long spaceflight [9, 10••, 11]. The authors pointed out crucial physiological parameters, such as maintenance of telomere length, genome stability, and epigenetic modification in response to extended space travel [11]. Studies in a mini-pig model confirmed that high doses of SPE-like radiation can cause skin damage, along with malfunction of the lung and heart [41, 42]. Furthermore, exposure to SPE radiation elicits deleterious effects on T cell activation, with mice becoming susceptible to bacterial infection [43].


Sun
A. Upper Panel
MOON
1.3 light seconds
MARS
4.35 light minutes
JUPITER
34.95 light minutes
SATURN
1.18 light hours
URANUS
2.52 light hours
NEPTUNE
4.03 light hours
PLUTO
4.6 light hours
INNER KUIPER BELT
4.02 light hours
OUTER KUIPER BELT
6.79 light hours
Time of Travel (Exposure)
Days
Months
Years
Decades
...
SPE
Increasing Flight Distance and Duration of Travel Outside of Lower Earth Orbit (LEO)
=
Increased Likelihood of Solar Particle Event (SPE) Exposure
=
Increased Likelihood of Developing Space Disease
Established Symptomatic: Progressive Acute and Chronic Radiation Damage, Multisystem Organ-Damage and Failure
Increasing Medical Need to Antagonize Space Disease with Increasing Travel Time
=
Physical Training and Radiation Toxicity Protection / Modulation / Mitigation
=
Shielding from Radiation and Therapy with Antioxidants and Tolerable Drugs
Novel Options: Stem Cell Therapy, e.g. Mesenchymal Stromal Cells (MSCs) Radioprotective / Repair Properties
MSCs Beneficial Properties
Reduce Systemic Inflammation ROS Production, Tissue Damage and Promote Tissue Regeneration
...
B. Lower Panel
Practical Challenges with MSCs
Mode of Clinical Delivery is Decisive for Feasibility, and Safe and Efficient Use in Space
...

◂**Fig. 1** Human interplanetary travel and MSC therapy in space. **A** Upper panel: Travel distance/duration that have to be anticipated during interplanetary travel, resulting in prolonged exposure to cosmic radiation and increasing the likelihood of exposure to solar particle events (SPEs) outside the lower Earth orbit (LEO). **B** Lower panel: SPE causes multiorgan damage and failure during long-term space flight, which may be counteracted in the future by mesenchymal stromal cell (MSC) therapeutics which have been shown to reduce systemic inflammation, ROS-production, tissue damage, and to promote tissue regeneration and recovery from acute and chronic radiation-damage. However, in particular, the mode of clinical delivery will be decisive for feasibility, safety, and efficacy of MSC therapeutics in space

Current Methods of Radiation Protection

The most common approach to avert the harmful impact of cosmic radiation during space travel is shielding, which establishes a protective physical barrier between the astronaut and space [44]. However, shielding is first of all costly, due to the great weight restriction posed on cargo brought into space, and second, only effective inside the LEO, since beyond LEO, the high-energy nuclei component of GCR (i.e. HZE ions) can penetrate shielding of space crafts [45, 46]. Hence, novel pharmacological agents have been introduced in space travel, to support ineffective shielding [40]. Meerman et al. discussed three specific types of pharmacological agents: 1 Radioprotectors (e.g. to reduce tissue damage before exposure), 2 Radiomodulators (e.g. to increase radio resistance of exposed tissues), and 3 Radiomitigators (e.g. to prevent tissue damage after exposure) [40]. However, the use of pharmacological agents may also induce impairment of normal tissue function; e.g. the angiotensin converting enzyme (ACE) inhibitor Captopril has demonstrated a positive effect in the reduction of radiation-induced complications in animal models, but its use entails a rare but serious risk of agioedema particularly in a low gravity environment [47]. The pharmacological agent Pentoxifylline, a xanthine derivate, has been identified as a remedy for both myocardial fibrosis and intermittent claudation, the muscle pain resulting from peripheral artery disease [48], but it is not yet well studied in radiation protection and has considerable side effects. In addition, physical exercise, antioxidants, and nutraceuticals provide a degree of non-toxic amelioration/protection against radiation toxicity. Several antioxidants are useful to protect DNA or tissues from the harmful oxidative stress and reactive oxygen species (ROS), which are generated during interaction between HZE and water molecules in biological tissues. In particular, Amifostine (first officially authorized radioprotector with activity based on catching free radicals and ROS to protect DNA and accelerate DNA repair selectively in healthy cells, but not tumour cells) [49–51], but also N-acetylcysteine (NAC), and hydrogen therapy, have shown positive effects against radiation induced tissue damage [40, 52]. However, considerable toxicity and clinical delivery aspects impair the wider use of Amifostine in daily practice [51]. Immune dysfunction is one of the common problems associated with spaceflight [1, 53]. To circumvent this, a combination of pharmacological, nutritional, and exercise interventions, such as stress reliving breathing exercise and personalized medications like Anti-histamine, Fexofenadrine, and Valacyclovir, are routinely prescribed for exploration space mission [54]. Polyclonal immunoglobulin and interleukin-2 are also used as the countermeasures to repair immune system impairment. However, these countermeasures also have some restrictions with respect to their stability, storage mass, or delivery in long-distance space travel. Importantly, all of these existing radioprotective methods are only partly effective and cannot yet provide optimal/maximal protection against radiation shock during long-duration space mission.

MSC Application as a Living Cellular Pharmaceutical in Space

As reviewed earlier [55–57], MSCs have shown promise as countermeasure for exposure to toxic radiation in preclinical animal models and first human clinical studies, e.g. for the treatment of radiation injury and radiation syndrome. For successful utilization of MSCs as a cell-based therapeutic in space travel, it is of importance to understand the requirements of these living therapeutic cells considering their optimal storage conditions, their mechanisms of action (MoA), and their pharmacokinetics and pharmacodynamics in this environment. In particular MSCs' mode of clinical delivery to patients should be considered as a key parameter, since it may impact greatly on therapeutic outcome, such as their safety and efficacy profile and MoA [2•, 3•, 4, 5, 36, 37].

While developing any personalized cellular therapy for astronauts, the foremost thing that needs to be considered is the radiation type/dose and flight duration. Post-flight chromosomal breaks were more repetitive in the Apollo astronauts compare to the Gemini astronauts [21], suggesting a direct correlation between the radiation dose/time and body's pathophysiological response. Importantly, clinical applications involving MSCs must thoroughly distinguish between chronic and acute radiation syndrome (CRS and ARS), since both entities do/may may have different molecular pathogenesis depending on the raditon dose and exposure time [57]. This may most certainly make adjustments in dose and timing of cellular therapy necessary. The majority of studies investigated the role of MSCs' in ARS, caused by radiation dose higher than 1 Gray (Gy), while CRS occurs due to chronic/repeated exposure to less than 1 Gy radiation. MSCs' role in chronic radiation syndrome is not well addressed so far. Hence, systemic study is required

to establish MSCs' therapeutic role in chronic radiation syndrome.

MSC Therapy in the Context of Space Travel: Radioresistance and Radioprotection

First research on stem cell-based therapy in the context of space exploration has been initiated, both for experimental studies and within the prospect of ameliorating space sickness [38, 57–60]. Some recent examples include a Bioculture System developed by NASA to conduct in-orbit experiments and the development of an integrated space laboratory, including a combined facility for cell culture and technologies for molecular biology (WetLab2) and other advanced tools [61]. Recently, Dr. Abba Zubair and team from Mayo Clinic studied the feasibility of cultivating MSCs in Space for their potential use during long-term space flight [38, 59].

Chinnadurai and DiCarlo reviewed the potential of MSCs as therapeutics for radiation injury and space sickness [55, 57] and another review by Nicolay and coworkers from Heidelberg University concluded that MSCs are radioresistant (as detailed below), and the authors outline the cellular and molecular mechanisms of MSCs' radioresistance and potential implications for clinical use [62]. MSCs' mesodermal differentiation capacity along with their potent immunomodulatory and pacrine properties make them ideal candidates for recovery of radiation induced injuries of the skin, intestine, brain, lung, liver, and heart [63]. For example, in an animal model of lethal ARS with severe weight loss, the secretome of injected placenta-derived MSCs (PLX-RAD of foetal origin) improved animal survival, the recovery of hematopoietic function, and the regain of weight-loss [64], and similar beneficial effects on multiple organ systems have also been observed in human patients under Earth gravity conditions, but also in animal models of simulated weightlessness [65–69].

MSCs can be formulated as 'off-the-shelf' living cellular drugs with multifactorial regenerative and immunomodulatory properties and low inherent immunogenicity [7, 70]. In addition, MSCs therapeutics can be applied through multiple means [2•, 3•, 4, 5]; e.g. they can be employed systemically or locally, and the cells can also be chemoattracted and migrate to sites of tissue damage in vivo, all of which may promote systemic and local immunomodulation and tissue repair by down-modulating inflammation and assisting tissue regeneration through multiple means. This may entail mitochondrial transfer and sequestration of repair signals, such as bioactive extracellular vesicles and various soluble and cell bound mediators [64, 71–73]. Thereby, MSCs can create a tissue protective environment at sites of tissue damage by secreting a plethora of immunomodulatory and regenerative paracrine mediators [7, 64], such as numerous short-lived immunomodulatory metabolites and diverse growth factors, such vascular endothelial growth factor and many others [7]. All of these properties make MSCs therapeutic candidates for a broad range of clinical indications [26, 74], such as skeletal diseases, cardiovascular diseases, autoimmune, inflammatory, and neurodegenerative disorders, many of whom are also of interest in the multifactorial symptomatic of space disease [1]. Hence, MSCs are envisioned to be utilized in space travel for the prevention of both acute and chronic tissue injury and multi-organ-system-failure.

Several studies identified that unlike with other BM-derived stem and progenitor cell populations, the in vitro survival of MSCs was not substantially impaired or indifferent to exposure of high doses of irradiation [57]. This radio-resistance of MSCs is more prominent under hypoxic conditions, which is manifested by increased proliferation, improved DNA damage repair, and enhanced long-term survival after exposure to ionizing radiation [75]. Furthermore, MSCs retain their stem cell features, such as plastic adherence and adipogenic, osteogenic, and chondrogenic differentiation potential even in exposure of high doses of ^{12}C carbon ion and even in 10 Gy of ionizing radiation [76, 77]. Therapeutic cell doses of MSCs could be maintained long-term in space in ambient low-temperature cryostorage systems in combination with appropriate radiation shielding, to prevent mutations and maintain their optimal function until thawing/recovery for clinical use [6]. MSCs actually possess radio-resistant properties to repair DNA double strand breaks induced by high doses of photon or ^{12}C particles by both non-homologous end joining and homologous recombination pathways [75, 78]. Akin to the radioprotective pharmaceuticals and antioxidants described above, MSCs were found to ameliorate tissue damage from oxidative stress by lowering ROS production [79]. Due to these preventive and regenerative properties in context of radiation damage, MSCs are considered as therapeutic candidate to alleviate the side effects of radio therapy [63]. Interestingly, an ongoing clinical study coordinated by Dr. Mohamad Mohty at INSERM in France (PRISME; NCT02814864) currently assesses MSC injections for the treatment of chronic radiotherapy-induced abdomino-pelvic complications and radiation-induced haemorrhagic cystitis. Collectively, these studies indicate that MSCs' radio-resistant and -protective properties may be exploited in the future to mitigate radiation-induced tissue damage during extended space missions (Fig. 1B).

Feasible Routes of Therapeutic Cell Delivery and Use of Fresh and Frozen Cells

Meta-analysis of existing clinical studies documents that MSCs exhibit an excellent safety in well-regulated clinical studies [37, 80–82]. Depending on the practical feasibility and specific treatment requirements, MSCs can be applied

either through local or systemic routes of administration [2•, 4, 5]. In particular, novel bio-instructive material-/hydrogel-guided approaches are generating an increasing interest to optimize both the safety and efficacy/potency of MSCs by positively modulating the functional properties of therapeutic MSC products and their concomitant biological effect [83]. Given the zero gravity environment in space, there is a certain need for comprehensive analysis of biodistribution, persistence, and fate of MSCs following various routes of cell administration. This applies for both, the in vivo distribution, but also to the cells behaviour in typical application devices, such as syringes and infusion bags, which may considerably alter their suspension, aggregation, and sedimentation properties, which are in turn all highly crucial aspects for effective cell delivery [84]. The currently established MSC delivery routes discussed below were established under normal gravity condition. Microgravity may interfere with the transplanted MSCs' biodistribution, hence their in vivo persistence and cellular fate. Furthermore, radiation shock may trigger gene and tissue alterations in the recipient (e.g. proinflammatory or necrotic tissue response), thus potentially resulting in altered therapeutic activity of MSCs towards the host, since cells will respond to in vivo signals. Hence, it is critical to understand MSCs' pharmacokinetics and pharmacodynamics before their application in long-space travel.

Local MSC Delivery is often performed to boost the immediate local activity/potency by increasing the engraftment of therapeutic cells at specific target sites. The simplest method for local MSCs delivery is topical application through introduction of a cell suspension or cell-containing hydrogel/patches directly onto the target area to be treated [4]. This method is preferred due to its technical simplicity and good safety profile for a range of indications, such as wound repair, to enhance skin graft survival, and for repair of defects in solid organs, such as heart, liver, or kidney [85], although it may be of use to treat surface wounds resulting from space sickness. In addition, intra-muscular injection (IM) is also considered to be a rather simple route of MSC delivery, although multiple cell injections with syringes may cause some transient discomfort and hematomas, which needs to be considered. However, IM delivery comes at the substantial advantage that it promotes the survival and dwell-time of implanted MSCs compared to other common routes, which may also be helpful to improve therapeutic outcomes in radiation injury and ARS [64, 65, 86]. In addition, the combination of therapeutic MSCs with bio-instructive hydrogels may further improve outcomes [83].

Systemic MSC Delivery Intravenous (IV) and intraarterial (IA) intravascular infusion are among the most popular approaches of MSC delivery, and IV application is commonly considered to be one of the most conventional and safest modes of cell delivery [37, 80–82]. Around 50% of human MSC clinical trials employ intravascular delivery for an extensive range of clinical disorders [3•, 5, 26, 37]. Nonetheless, a plurality of reports has identified that the IV-applied MSCs are rapidly trapped in the lungs and cleared shortly afterward [87], which may be related to triggering of the instant-blood mediated inflammatory reaction (IBMIR) in response to infusion of highly procoagulant tissue factor (TF/CD142) expressing MSC therapeutics with insufficient hemocompatibility [37, 88–93] and concomitant suboptimal efficacy in some clinical indications due to early cell destruction [2•, 4, 5]. Since their paracrine MoA supports MSC therapeutic activity/potency, a reduced lifespan of grafted cells may debilitate their therapeutic activity [2•, 3•]. A recent preclinical study identified that repeated IV delivery of a maximally tolerated dose (50 million cells/kg body weight) of fit MSCs failed to affect colitis clinical outcomes [3•], while another research group identified beneficial effects of IV infused MSCs in the reduction of lethal sepsis [94]. This discrepancy may be explained by the process of efferocytosis [6, 89, 95, 96], where lung-resident macrophages rapidly phagocytose more than half of the lung-trapped MSCs and their residue to be skewed in an anti-inflammatory M2 profile to produce interleukin-10 (IL-10), thereby reducing tissue inflammation [94]. This report is corroborated by another preclinical study where intra peritoneal (IP) or IV-delivered apoptotic MSCs were effective in improving GvHD outcomes via the secondary efferocytotic response [97, 98]. Compared to the IV approach, IA application can be more effective in certain indications, as it can reduce cell-trapping in the lungs and thus promote cell engraftment at the target site, e.g. the ischemic leg [99]. However, there are also reports showing a risk for adverse embolic effects related to this approach [100, 101]. MSCs targeted to the brain via IA delivery demonstrated a risk of stroke [101]. For utilizing the IA approach, cell size/cell aggregate removal, cell dose, and infusion speed must be carefully adjusted to prevent cell embolization and tissue ischemia [4]. Though IP or subcutaneous route of MSC delivery are not very common, in some preclinical studies, they improved the recovery from various indications; e.g. while the maximum tolerated IV delivered MSC dose was ineffective to improve toxic colitis in mice, SC or IP delivered MSCs demonstrated a positive therapeutic effect on colitis clinical and pathologic endpoints [3•].

Cardiovascular Regenerator Systems An entirely different approach to deliver MSCs' beneficial therapeutic properties is to employ MSC-loaded dialyzer-based CVR systems that are currently developed as intensive care support units to reduce inflammation and promote regenerative pathways in severely compromised patients [102–106]. These would

be of particular interest in long-distance space missions, since units could be prefabricated and loaded with MSCs to be used as rescue module for acute incidents or regular spaced support to promote regenerative pathways in addition to training and other active countermeasures to promote astronaut well-being.

Enhancement of MSC's Therapeutic Activity

Clinically relevant engineering approaches to improve MSC bioactivity and safety that may also be beneficial in the context of space exploration are in principle almost countless [92, 106, 107], but here we wish to outline some key aspects that have shown promise in recent years.

Integrated Systems According to numerous mechanistic studies, MSCs deploy local and systemic immunomodulatory effects via the secretion of numerous paracrine soluble factors [7]. Studies by Dr. Zubair and colleagues are now certain that MSCs can be cultured and expanded in space microgravity with intact morphological and regenerative properties [38, 59]. However, for the treatment of tissue injury, single or multiple doses of more than 100 million cells are required, which are rather difficult to grow at a time, particularly in space. Here, a prefabricated system, either preloaded or to be loaded, with cryobanked 'off-the-shelf' MSC batches ready for therapeutic use, such as the CVR system introduced above [102–106], would provide a very elegant solution to rapid availability without prior need for cell expansion in space. Preclinical studies have also tested culture rescued log phase growth MSCs to get a more optimal therapeutic benefit [95]. Here, a closed cartridge CVR system would also allow for short culturing/revitalization of cryostorage derived cells to boost their metabolic function and improve their hemocompatibility [104].

Freeze-Thawing In many human clinical trials, pre-banked cryopreserved allogeneic MSCs are used, which are thawed immediately before transplantation [6]. However, immediately post thawing therapeutic cells may possess partially defective immune functionality/metabolic activity and in addition express typical cell injury markers that promote cell clearance upon infusion [6, 89, 108]. Thawed cells readily derived from cryostorage display reduced in vivo persistence due to increased susceptibility to T cell mediated lysis [6, 109], which is in part due to the expression of the same altered cell surface features that also promote the triggering of IBMIR, such as phosphatidylserince exposure resulting from cell membrane asymmetry post thawing [6, 89, 104, 110]. Short in vivo persistence of post-thawed MSCs is associated with impaired cell-dependent functionality [3•]. Importantly, while improper methods of cryopreservation and thawing can cause damage of MSCs, optimized cryomedia and freeze-thawing procedures may yield improved outcomes, and culture rescue of MSCs for 16- to 24-h post-thaw can completely reverse the cryoinjury effect [6].

Hemocompatiblity Their immunomodulatory and regenerative properties and in part also their lineage differentiation form the basis of MSCs' therapeutic activity/potency. As outlined above, the hostile tissue environment encountered by MSCs after in vivo delivery promotes cellular apoptosis and triggering of IBMIR with concomitant therapeutic cell graft destruction and rejection, which is furthermore affected by patient-specific parameters [2•, 5, 36]. Spaceflight and microgravity may alter coagulation parameters, promote hypercoagulability, and induce venous and/or coagulation pathology, particularly in the cephalad venous system [111]. This may be associated with altered/increased triggering of IBMIR responses to systemically infused TF/CD142-bearing cell products and thus altered safety profiles, cell persistence, and functionality. To improve MSCs in vivo persistence, different cellular or genetic modification strategies and preconditioning approaches have been studied extensively in the past [5]. The modification/downmodulation of MSCs' expression of highly procoagulant TF/CD142 has been identified as a key target to improve their hemocompatibility for intravascular applications [37]. In addition, TF/CD142 knockout and downmodulation strategies, or cell coating with hemocompatible surfaces, such as macromolecular-heparin-conjugates, as well as suitable patient thromboprophylaxis, are envisioned [5], which must be carefully reviewed and re-evaluated for operability in the space environment.

Alloimmunity Although MSCs are commonly considered to be hypoimmunogenic, recent studies have better identified that MSCs are rather 'immune-evasive' than 'immune-privileged' [70]. However, using allogeneic MSCs as the 'off-the-shelf' product have many advantages, especially that a substantial amount of healthy allogeneic MSCs is readily available at the time of need, while for the autologous MSCs, it is difficult to collect the similar amount of good quality cells within short period of time, although this benefit may come at the cost of anti-donor immune responses [70, 112, 113]. Given the currently still fairly small crew number of astronaut crews, cell banks of HLA-compatible/matched products could be prepared in advance. Mechanistically, it appears to be beneficial for the therapeutic outcome to protect MSCs from allo-rejection [3•]. Different approaches have been identified so far to protect allogeneic MSCs from recognition of host cell immunity, such as the temporary administration of immunosuppressive drugs along with the therapeutic cells or 'immune-editing' to genetically prevent MHC II expression are some potential avenues to improve the in vivo persistence of allogeneic MSC products.

Metabolism Hypoxia preconditioning and careful adjustment of nutrient supply may be another approach to promote MSC's persistence before in vivo application and hence their therapeutic potency in human clinical trials, since it may reduce cell starvation upon transplantation into oxygen and nutrient poor tissue environments [114]. In addition, it has been recognized that transplanting integrin-linked kinase (ILK) overexpressed MSCs into an ischemic myocardium model, improved myocardial damage recovery through rapid angiogenesis [115]. Since myocardial damage is a common phenomenon in radiation injury, it can be speculated that ILK overexpresses MSCs could serve as a potential therapeutic against radiation-induced myocardial disease.

Conclusions

The harmful effect of radiation exposure on internal organs and tissue function is a major concern for long-term manned missions. Therefore, space agencies emphasize research to evaluate the health risks that astronauts experience during and after long-distance space travel beyond the LEO [1]. Exploring novel strategies to ameliorate space radiation-induced injury is equally important. Although shielding approaches and pharmacological agents are available, these may not be very effective for the HZE component of GCR beyond LEO, particularly during interplanetary travel. Hence, developing alternate protective strategies is one of the newest challenges in space research. Presently, researchers are making first efforts to implement stem cell-based therapy in space travel. Here, MSC-based therapeutics provide considerable promise, due to their profound regenerative and immunomodulatory properties, and their therapeutic potential to alleviate radiation injury/ARS. Although MSCs bear great promise, their clinical development is still in the early phase and needs to overcome many practical challenges to implement their full potential. The enhancement of MSCs' therapeutic properties (e.g. anti-apoptotic, antioxidation, proangiogenic, immunomodulation, regeneration, and hemocompatibility) before infusion, their optimized clinical delivery to patients, but also novel cellular modification/licensing approaches, e.g. by employing pharmaceutical approaches or cytokine pre-activation and genetic engineering, offers new avenues to further advance MSC-based therapy in space applications. MSCs' full potential as a living cellular pharmaceutical depends upon MSCs in vivo persistence inside the host, the route of clinical delivery, culture conditions, and also the host tissue environment, which all influence their in vivo persistence. Although in human clinical trials IV administration is the most favoured conventional approach, IV delivered cells are cleared rapidly by triggering of the innate and adaptive immune cascades, e.g. IBMIR, T cell allorecognition, and efferocytosis by host phagocytes, which may considerably impair cell-dependent functionality. Preliminary studies have identified that microgravity is not detrimental, but may even have a beneficial effect on MSCs' proliferative and therapeutic capacity, thus indicating potential to employ therapeutic approaches based on culturing MSCs during space travel, such as haemodialysis-integrated CVR systems. We here anticipate a promising future for MSC therapy in alleviating radiation injury in long-term manned space travel.

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Declarations

Conflict of Interest Jayeeta Giri and Guido Moll declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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