Perspective

A second space age spanning omics, platforms and medicine across orbits

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The recent acceleration of commercial, private and multi-national spaceflight has created an unprecedented level of activity in low Earth orbit, concomitant with the largest-ever number of crewed missions entering space and preparations for exploration-class (lasting longer than one year) missions. Such rapid advancement into space from many new companies, countries and space-related entities has enabled a 'second space age'. This era is also poised to leverage, for the first time, modern tools and methods of molecular biology and precision medicine, thus enabling precision aerospace medicine for the crews. The applications of these biomedical technologies and algorithms are diverse, and encompass multi-omic, single-cell and spatial biology tools to investigate human and microbial responses to spaceflight. Additionally, they extend to the development of new imaging techniques, real-time cognitive assessments, physiological monitoring and personalized risk profiles tailored for astronauts. Furthermore, these technologies enable advancements in pharmacogenomics, as well as the identification of novel spaceflight biomarkers and the development of corresponding countermeasures. In this Perspective, we highlight some of the recent biomedical research from the National Aeronautics and Space Administration, Japan Aerospace Exploration Agency, European Space Agency and other space agencies, and detail the entrance of the commercial spaceflight sector (including SpaceX, Blue Origin, Axiom and Sierra Space) into aerospace medicine and space biology, the first aerospace medicine biobank, and various upcoming missions that will utilize these tools to ensure a permanent human presence beyond low Earth orbit, venturing out to other planets and moons.

The launch of the Russian satellite Sputnik in 1957 and the establishment of the National Aeronautics and Space Administration (NASA) in 1958 marked the beginning of the first space age. This era not only changed humanity, but also reshaped our relationship with our Moon, the solar system and the search for new stars. The USSR and the USA fiercely competed in space launches (Fig. 1, inset) during the cold war, which evolved from short missions to the first space stations (Salyut 1, launched by the USSR and Skylab, launched by the USA). Eventually, more countries created capacity for space exploration (Fig. 1), which introduced a wider range of genetic, medical and ethnic backgrounds among the humans who have flown into space. This led to increased interest in the effects of spaceflight on human physiology.

Sex-specific differences in the effects of spaceflight on humans have gained attention as more women have entered space. The USSR were first to send a woman to space—Valentina Tereshkova, in 1963[1]—followed by the Americans, with Sally Ride in 1983. Notably, female astronauts appear to be less affected by spaceflight-associated neuro-ocular syndrome than male astronauts, but are more severely affected by other modalities, such as vascular responses and possible cancer risk[2]. However, comprehensive studies on cell-specific and genetic changes in both sexes only began in 2021, revealing differences crucial for mission planning[3–5].

Astronaut selection, traditionally performed by government agencies such as NASA, JAXA and ESA, expanded from considering candidates from the US military in 1959 to include scientists in 1962[6]. Current criteria for astronaut selection typically involve citizenship, advanced degrees and physical, cognitive and stress testing. The involvement of the private sector, starting with Orbital Sciences Corporation's Pegasus mission in 1990, has reshaped space exploration (Pegasus XL; https://go.nature.com/3y5oxhk). The contributions of the private sector to spaceflight technology and crew health research expanded with the entry of companies such as Blue Origin, Virgin Galactic and SpaceX. In 2021, SpaceX Inspiration4 (I4) marked the first fully private, crewed orbital mission, emphasizing the growing trend of civilian astronauts[7–9]. Subsequently, 2022 and 2023 have set records for the most launches into space by both commercial and government agencies[10] (n = 188 and n = 196, respectively). The SpaceX Starship, the largest rocket ever built, reached orbit in 2024, highlighting the accelerated pace of spaceflight technologies and new economies for space exploration[11].

These developments in spaceflight are not just a difference of scale—they represent a substantive difference in the speed, type and degree of access to space. For example, after more than 20 years of continuous human presence in space onboard the solitary International Space Station (ISS), there is now another orbiting space station (Tiangong) from the Chinese National Space Administration (CNSA) and 5 orbital platforms are being planned by Axiom, Northrop Grumman, Sierra Space-Blue Origin, VAST and Voyager-Nanoracks. Furthermore, additional research platforms are currently in development beyond low

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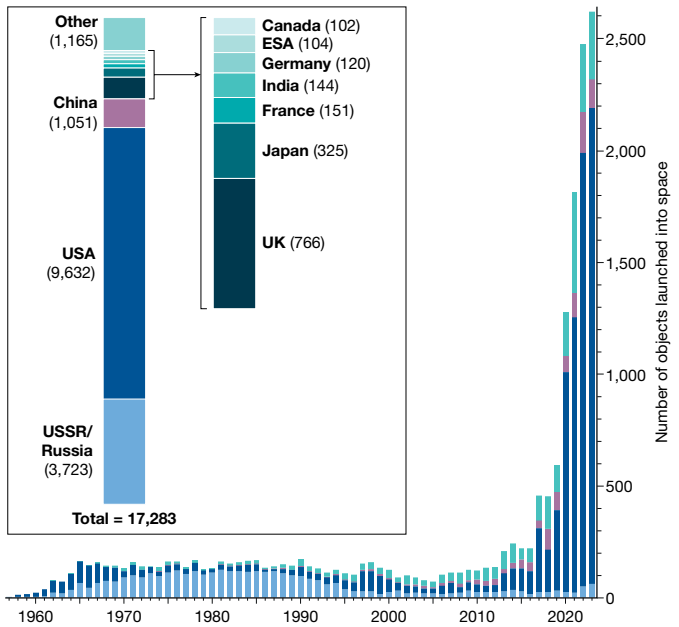

Fig. 1 | A historic overview of space launches. Inset, the launches that defined the first space age, from 1957 to 2022, broken down by country of origin. Main, the exponential increase in the number of launches per year, increasingly driven by commercial launches, marks the second space age.

Earth orbit (LEO), including the NASA-led Lunar Gateway space station orbiting the Moon, which will have Canadian Space Agency (CSA), ESA, Mohammed Bin Rashid Space Centre and JAXA as partners, and permanent lunar habitats from the NASA Artemis programme, as well as lunar habitats from the CNSA and ROSCOSMOS (led by the Russian government). By the late 2030s, the Mars Base Camp orbital platform (from Lockheed Martin) is planned to orbit around Mars, providing continual access to the surface[12] (Table 1).

These accelerating trends have arguably created a second space age that features key differences from the first space age. Specifically: (1) the commercial spaceflight sector is now leading many launches and missions; (2) there is a log-level increase in the number of countries participating in space exploration (Fig. 1); (3) advanced cellular and molecular studies of the human body's spaceflight response has surpassed the number of publications from previous missions such as the NASA Twins Study[13]; (4) biomedical, behavioural and omics data from astronauts can now be accessed through a biobank and biorepository[8]; (5) there is increased crew heterogeneity across age, sex and race; and (6) a continued human presence will extend beyond LEO, including lunar bases and planetary missions (Table 1). This second space age enables 'precision astronaut medicine' and thus, the opportunity to create personalized countermeasures for astronauts. In addition, accessible astronaut biomedical data in biobanks benefits research in both space- and Earth-based contexts[14,15], similar to the utility of the AllofUs Research Program and the UK Biobank.

In this Perspective, we highlight research from the Space Omics and Medical Atlas (SOMA) across orbits package of manuscripts, data, protocols and code, which features data collected from SpaceX I4 crew members, JAXA studies, NASA and ESA astronauts, and a comparison of these results with a large body of model organism data, cellular profiles, computational models and countermeasures. The I4 mission, the first all-civilian spaceflight, provided unprecedented insights through multi-omics (including RNA sequencing (RNA-seq), microbiomics and proteomics) and diverse medical assessments (neurobehavioural, cognitive and environmental). This mission generated nearly 3,000 samples and hundreds of terabytes of data, constituting the most extensive dataset for human space exploration to date, and the first mission with public access to paired astronaut data (through the SOMA portal) and samples[8,15] (biobank). In addition, The SOMA package includes blood measurements from the 1960s Mercury missions up to recent commercial missions in 2024, and features a wide range of molecular and cellular assays across humans, model organisms and ground-based simulations[16,17,18] (for example, NASA Space Radiation Laboratory) performed by investigators across more than 100 institutions. These datasets show changes at the cellular, tissue, organismal and systematic levels (Table 2), and begin to map differences between populations (for example, stratified by age and sex) and link specific countermeasures to each astronaut. We describe here the specific changes observed at each modality of biology, detail their significance and link them to future missions and plans for the coming decades, with the aim of creating a guide for potential countermeasures and tools that are essential for ensuring safe human space travel, particularly as mission durations, risks and radiation levels increase.

Cellular adaptations in response to spaceflight

Spaceflight introduces hazards that result in diverse cellular and molecular changes[19], primarily influenced by two factors: space radiation exposure and microgravity. Galactic cosmic radiation (GCR) is an unavoidable aspect of short- or long-term space missions, and exposes astronauts to various atomic nuclei containing high linear energy transfer (LET) particles such as ^{56}Fe and ^{28}Si, which pose significant health risks. DNA damage responses to radiation exposure include distinct imprints on the human genome, transcriptome and chromatin structure[20,21]. Understanding these effects in the space environment is crucial for minimizing detrimental health outcomes[22].

Perdyan et al.[23] conducted a computational multi-omics analysis, investigating the effects of GCR on epigenetic[24,25] and transcriptomic patterns using in vitro data from different bronchial epithelial cell lines that were exposed to space radiation, in vivo data from mice exposed to whole-body space radiation, and astronaut data from JAXA studies[26] obtained from the NASA Open Science Data Repository (OSDR; https://osdr.nasa.gov/bio/)/GeneLab (https://genelab.nasa.gov/) platform[27]. Results showed that ^{56}Fe induced DNA hypermethylation, whereas ^{28}Si and X-ray exposure led to global DNA hypomethylation. Differentially methylated sites primarily accumulated in the nuclear periphery, with minor DNA methylation changes in euchromatic regions. Persistent epigenome and transcriptomic changes that lasted up to four months after landing were induced by ^{56}Fe, but not by ^{28}Si, in model organisms exposed to simulated GCR and in astronauts from the JAXA study. The possible mechanisms behind the distinct ^{56}Fe and ^{28}Si responses will be examined in future studies.

Spaceflight-induced changes also extend to telomeres, the nucleoprotein complexes at chromosomal termini essential for maintaining genome stability. Previous work showed telomere elongation in NASA astronauts[13,28,29], and recent studies shed light on the probable mechanisms behind this phenomenon[8,30]. Increased levels of telomeric RNA (TERRA) in spaceflight samples suggest that it has a role in facilitating telomeric recombination-mediated repair through the telomerase-independent alternative lengthening of telomeres pathway[31], and telomeric RNA may also form dipeptide-repeat signalling proteins[32]. These findings have broad implications for scenarios involving persistent telomeric DNA damage, such as space radiation exposure.

Chromosomal and telomeric damage induced by the space environment also has a direct effect on immune-related dysfunction. Burke et al.[33] explored the effects of simulated GCR on mouse models, revealing sexually dimorphic immune and endocrine responses. RNA sequencing also indicated distinct sex-specific responses, with female mice showing more efficiently regulated inflammation profiles compared with male mice, which matches gene expression data from the I4 crew, and underscores the importance of personalized translational approaches for astronauts on exploration missions.

Table 1 | Upcoming LEO and interplanetary missions

Destination	Mission name	Mission details	Agency	Agency type	Mission type	Links
Asteroids and Kuiper Belt	DART	DART launch (2021); asteroid Didymos impact (2022)	NASA	Government	Flyby	https://science.nasa.gov/mission/dart/
	DART and Hera	Hera launch to visit DART (2024); Hera arrives at Didymos site (2026)	ESA	Government	Flyby	https://www.heramission.space
	Lucy	Launch (2021); inner–main belt (2025); L4 Trojan Cloud (2027); L5 Trojan Cloud (2033)	NASA	Government	Flyby	https://science.nasa.gov/mission/lucy/
	Hayabusa2	Launch (2014); asteroid Ryugu sample return (2020); asteroid (98943)2001 CC21 (2026); asteroid 1998 KY26 (2031)	JAXA	Government	Flyby	https://science.nasa.gov/mission/hayabusa-2/
	New Horizons	Launch (2006); Pluto (2015); Arrakoth (2019); Kuiper belt (2023 onwards)	NASA	Government	Flyby	https://science.nasa.gov/mission/new-horizons/
	OSIRIS-Rex	OSIRIS-Rex asteroid sample return: launch (2016); return (2023)	NASA	Government	Sample return mission	https://science.nasa.gov/mission/osiris-rex/
	Psyche	Launch of Psyche asteroid probe (2023); arrival (2026); completion (2028)	NASA	Government	Orbiter	https://www.jpl.nasa.gov/missions/psyche
Exoplanets	Starshot	Launch of Breakthrough Starshot (2036); arrival (2061); signal returns (2065)	Breakthrough Initiatives	Non-government	Flyby	https://breakthroughinitiatives.org/initiative/3
Gas giants	Dragonfly	Launch of Dragonfly lander (2027); arrival on Titan (2034)	NASA	Government	Lander	https://dragonfly.jhuapl.edu
	Europa Clipper	Launch (2024); arrival (2028)	NASA	Government	Orbiter	https://europa.nasa.gov
	PERSEUS	Launch (2031); arrival (2043)	NASA	Government	Orbiter	https://ntrs.nasa.gov/citations/47115782563137
	JUICE	Launch (2023); arrival (2030); orbit Ganymede (2034)	ESA	Government	Orbiter	https://www.esa.int/Science_Exploration/Space_Science/Juice
	Tianwen-4	Launch (2029); Jupiter orbit (2035); Uranus flyby probe (2045)	CNSA	Government	Orbiter and flyby	
LEO	Gaganyaan	Launch (2023)	ISRO	Government	Crewed spacecraft	https://www.isro.gov.in/Gaganyaan.html
	Space tours	First tour (2023)	Virgin Galactic	Non-government	Crewed spacecraft	https://brochure.virgingalactic.com/spaceflight/
Mars	Mars Base Camp	Launch (2028); return (2031)	Lockheed Martin	Non-government	Deep space habitat	https://www.lockheedmartin.com/en-us/products/mars-base-camp.html
	Hope	Launch (2020); arrival (2021); completion (2024)	United Arab Emirates Space Agency	Government	Orbiter	https://www.emiratesmarsmission.ae/hope-probe/instruments/
	Mangalyaan 2 and Mars Orbiter Mission	Launch (2024)	ISRO	Government	Orbiter	https://www.youtube.com/watch?v=H7NReDaplks and https://www.isro.gov.in/MarsOrbiterMissionSpacecraft.html
	Perseverance	Launch (2020); arrival (2021); collections (2021–2025).	NASA	Government	Rover	https://mars.nasa.gov/mars2020/
	Mars Sample Return	Launch (2026); arrival (2028); return (2032)	NASA	Government	Retrieval	https://mars.nasa.gov/msr/
	Tianwen	Tianwen-1 launch (2020); arrival (2021); Tianwen-2 (2025); Tianwen-3 sample retrieval (2030)	CNSA	Government	Rover	https://nssdc.gsfc.nasa.gov/nmc/spacecraft/display.action?id=2020-049A
	MMX	Launch (2024); orbit (2025); return (2029)	JAXA	Government	Orbiter	https://www.mmx.jaxa.jp/en/
	Rosalind Franklin	Launch (2028); arrival (2030)	ESA	Government	Rover	https://www.esa.int/Science_Exploration/Human_and_Robotic_Exploration/Exploration/ExoMars/ExoMars_rover
	Starship: uncrewed lander	Launch (2027)	SpaceX	Non-government	Uncrewed lander	https://www.spacex.com/vehicles/starship/
	Starship: crewed lander	Launch first crew (2027)	SpaceX	Non-government	Crewed lander	https://www.spacex.com/vehicles/starship/

Continued

Destination	Mission name	Mission details	Agency	Agency type	Mission type	Links
Moon	Argonaut	Argonaut 1 (2031); Argonaut 2 (2033); Argonaut 3 (2035)	ESA	Government	Uncrewed spacecraft	https://www.esa.int/Science_Exploration/Human_and_Robotic_Exploration/Exploration/Argonaut
	Artemis	Artemis 1 (2022); Artemis 2 (2025); Gateway (2026); Artemis 3 (2027); Artemis 4 (2030); Artemis 5 (2031); Artemis 6 (2032)	NASA	Government	Uncrewed spacecraft	https://www.nasa.gov/humans-in-space/artemis/
	Moonlight	Moonlight (2024)	ESA	Government	Uncrewed satellites	https://www.esa.int/ESA_Multimedia/Videos/2022/11/What_is_ESA_s_Moonlight_initiative
	Chandrayaan	Chandrayaan-3 (2023); Chandrayaan-4 (2028); Chandrayaan-5 (2030); Chandrayaan-6 (2032)	ISRO	Government	South pole, drilling and sample return missions	https://www.isro.gov.in/Chandrayaan3_Details.html
	Chang'e	Chang'e 5 (2020)	CNSA	Government	Sample return mission	https://nssdc.gsfc.nasa.gov/nmc/spacecraft/display.action?id=2018-103A
	Chang'e	Chang'e 6 (2025)	CNSA	Government	Lander	https://nssdc.gsfc.nasa.gov/planetary/lunar/cnsa_moon_future.html
	Chang'e	Chang'e 7/Rashid II (2026)	CNSA and MBRSC	Government	Lander	https://nssdc.gsfc.nasa.gov/planetary/lunar/cnsa_moon_future.html
	Chang'e	Chang'e 8 (2027)	CNSA	Government	Lander	https://nssdc.gsfc.nasa.gov/planetary/lunar/cnsa_moon_future.html
	ILRS	Launch (2026)	CNSA and ROSCOSMOS	Government	Lander	https://www.cnsa.gov.cn/english/n6465652/n6465653/c6812150/content.html
	Intuitive Machines (IM)	IM-1 (2024); IM-2 (2025); IM-3 (2026)	Commercial	Non-government	Lander	https://www.intuitivemachines.com/
	Russia lunar	Launch test and lunar soil return (2027)	ROSCOSMOS	Government	Lander	
	Russia lunar	Launch crew (2029)	ROSCOSMOS	Government	Lander	
	SLIM	SLIM (2022)	JAXA	Government	Lander	https://global.jaxa.jp/projects/sas/slim/
	VIPER	Launch (2024)	NASA	Government	Lander	https://science.nasa.gov/mission/viper
Venus	DAVINCI	Launch (2029)	NASA	Government	Flyby	https://ssed.gsfc.nasa.gov/davinci/
	Envision	Launch (2031)	ESA	Government	Orbiter	https://www.esa.int/Science_Exploration/Space_Science/EnVision_factsheet
	Vertias	Launch (2031)	NASA	Government	Orbiter	https://www.jpl.nasa.gov/missions/veritas
Mercury	BepiColombo	Launch (2018); landing (2025)	ESA and JAXA	Government	Orbiter	https://www.esa.int/Science_Exploration/Space_Science/BepiColombo

Current mission plans include those led by non-government actors, NASA (government (US)) and non-US governments. Asteroid-related missions will be conducted mainly by NASA and the European Space Agency (ESA) (https://www.heramission.space/; https://science.nasa.gov/mission/lucy/; https://science.nasa.gov/mission/osiris-rex/; https://psyche.asu.edu/; https://nssdc.gsfc.nasa.gov/nmc/spacecraft/display.action?id=2005-014A). The exoplanets missions will be conducted by Breakthrough Initiatives (https://breakthroughinitiatives.org/initiative/3). Gas giants missions will be conducted by NASA (https://dragonfly.jhuapl.edu/; https://europa.nasa.gov/), ESA (https://www.esa.int/Science_Exploration/Space_Science/Juice) and China National Space Administration (CNSA). LEO missions listed here will be done by Indian Crewed Spaceflight (Indian Space Research Organisation (ISRO); https://www.isro.gov.in/Gaganyaan.html) and Virgin Galactic (https://brochure.virgingalactic.com/spaceflight/). Several agencies are planning Mars missions, including Lockheed Martin (https://www.lockheedmartin.com/en-us/products/mars-base-camp.html), United Arab Emirates Space Agency (https://www.emiratesmarsmission.ae/hope-probe/instruments/), ISRO[110], NASA (https://mars.nasa.gov/mars2020/; https://science.nasa.gov/mission/mars-sample-return/), CNSA (https://nssdc.gsfc.nasa.gov/nmc/spacecraft/display.action?id=2020-049A), Japan Aerospace Exploration Agency (JAXA; https://www.isas.jaxa.jp/en/), ESA (https://www.esa.int/Science_Exploration/Human_and_Robotic_Exploration/Exploration/ExoMars/ExoMars_rover) and SpaceX (https://www.spacex.com/). The Moon missions will be conducted by the NASA Artemis programme (with support from ESA; https://www.nasa.gov/specials/artemis/index.html; https://www.esa.int/Science_Exploration/Human_and_Robotic_Exploration/Orbiter/Artemis_I; https://www.esa.int/Science_Exploration/Human_and_Robotic_Exploration/Orbiter/Artemis_II), China (CNSA) and ROSCOSMOS[111] (https://nssdc.gsfc.nasa.gov/planetary/lunar/cnsa_moon_future.html) and JAXA (https://global.jaxa.jp/projects/sas/slim/). Both NASA (https://ssed.gsfc.nasa.gov/davinci/; https://www.jpl.nasa.gov/missions/veritas) and ESA (https://www.esa.int/Science_Exploration/Space_Science/EnVision_factsheet) are planning Venus missions. There is also a joint ESA and JAXA Mercury mission (https://www.esa.int/Science_Exploration/Space_Science/BepiColombo). Rosalind Franklin is part of the ExoMars programme. DART, Double Asteroid Redirection Test; PERSEUS, Plasma Environment, Radiation, Structure, and Evolution of the Uranian System; JUICE, Jupiter Ice moons explorer at Jupiter, Ganymede, Callisto and Europa; MMX, Martian Moons Exploration; ILRS, International Lunar Research Station; VIPER, Volatiles Investigating Polar Exploration Rover.

To further explore immune dysregulation in spaceflight, an extensive review[5] highlighted the severe effects of the space environment on macrophages, central innate immune cells that are crucial for antigen removal and directing adaptive immune responses[13,34]. A single-cell multi-omics and cytokine analysis of the 14 crews has identified 17 cytokines and chemokines related to inflammation and muscle homeostasis whose levels increased after spaceflight, and revealed changes in gene expression, chromatin accessibility and T cell and B cell

Table 2 | The Space Omics and SOMA across orbits packages

	Main assays	Key cellular and tissue changes	Ref.	Astronaut data
Cellular				
Mitochondria	RNA-seq	Plasma cell-free RNA maps indicating mitochondrial dysfunction	47	JAXA
	WGS	Mitochondrial DNA in plasma and genome stability	30	JAXA, I4 and NASA Twin
Immune cells	scRNA-seq	Immune dysfunction in space and simulated microgravity	35	JAXA, I4 and NASA Twin
	Single-cell multi-omics	Inflammation and chromatin changes in monocytes	3	I4
	Sex-specific immunomes	Sexually dimorphic immune and endocrine kinetics	33	None
	Behavioural assays and flow cytometry-based immune cell profiling	Decreased monocyte-driven changes over time	112	None
	RNA-seq	Haemoglobin dysregulation	113	JAXA, I4 and NASA Twin
Chromosomes and telomeres	WGS and RNA-seq	Increased telomeric RNA and telomere length changes	30,31	I4 and NASA Twin
	Epigenetics and transcriptomics	DNA methylation changes	8,23	I4 and JAXA
Epigenetic changes	Epitranscriptomics	RNA methylation increases and shifts	114	I4 and NASA Twin
Endocrine effects	Multi-omics	Changes in insulin and oestrogen signalling	4	JAXA and I4
Organs and tissues				
Heart	Multi-omics and western blotting	Cardiac fibrosis and miRNA increases	61	JAXA and I4
	CHIP	Increased CHIP hazard ratios	115	None
		CHIP changes from spaceflight	30	I4 and NASA Twin
Skin	Spatial multi-omics	Inflammatory skin changes	57	I4 and NASA Twin
	Transcriptomics	Skin health dysfunction	56	JAXA, I4 and NASA Twin
Skeletal muscle	Bioreactor	Development of muscle countermeasures	54	None
	Transcriptomics	Sarcopaenia	52	JAXA and I4
Brain	Spatial transcriptomics	Neurodegenerative disease	59	None
	Multi-omics and exosome profiling	Oxidative stress and blood–brain barrier disruption	60	I4 and NASA Twin
	Behavioural and neurochemical assays	Psychomotor vigilance and neurotransmitter disruption	58	None
Kidney	Multi-omics and spatial transcriptomics	Kidney dysfunction	63	JAXA, I4 and NASA Twin
Systemic, host–microorganism and whole-body effects				
Whole body	Biospecimen protocols	Blood, urine and skin	9	I4 and NASA Twin
	Biobank and data repository	SOMA	8	I4, NASA Twin and JAXA
	Physiological and molecular assays	Crew differences and I4 mobile imaging	7	I4 and NASA Twin
Microbiome	Metagenomics and metatranscriptomics	Microbial exchange	74	I4 and NASA Twin
	Metagenomics	Microbial adaption to space	72	None
	Metagenomics	Microbial tracking on the ISS	116	None
Countermeasures				
Drugs	RNA-seq and treatments with miRNA inhibitors	Immune and mitochondrial activation	61,62	JAXA, I4 and NASA Twin
Genes	WGS, RNA, CRISPRa and CRISPRi	Protective alleles and data modelling	97,99	I4 and NASA Twin
Computational and omics tools				
AI	Multi-omics and machine learning	Calcium uptake in muscles	117	None
	Machine learning and transcriptomics	Liver dysfunction	118	None
Omics analysis	Transcriptomics	Muscle degradation	119	I4
	Machine learning, CRISPR and transcriptomics	Liver dysfunction	92	None
Perspectives, reviews and ethics				
	Macrophage alterations in response to spaceflight		5	None
	AI-supported precision health in space		120	I4 and NASA Twin
	AI in space research		121	None
	Ethics for commercial spaceflight		98	I4
	Open science integration for space biology research		122	I4, NASA Twin and JAXA
	Inspiration4 data availability on NASA's open science platform		123,124	I4
	Women's health and reproductive systems		125	I4

The research and papers discussed in this manuscript are highlighted and categorized by biological components: cellular, organ and tissue, and whole body. In addition, we categorize the countermeasures and computational research separately. Finally, the annotation of astronaut data is included in the manuscripts. AI, artificial intelligence; CHIP, clonal haematopoiesis of indeterminate potential; CRISPRa, CRISPR-mediated transcriptional activation; CRISPRi, CRISPR interference; miRNA, microRNA; scRNA-seq, single-cell RNA-seq; WGS, whole-genome sequencing.

receptor immune repertoire in response to spaceflight[3,8,9]. Differentially expressed genes were enriched for immune-metabolic pathways as well as chromatin modifications, and the immune cell types that were most affected by spaceflight were CD14 and CD16 monocytes. Integration with microbiome abundance data from the same crews has identified differentially expressed genes in immune cells that are associated with shifts in taxonomy and viral activation in the microbiome[3].

In addition to space radiation, microgravity can also affect the entire human immune system[35]. scRNA-seq analysis of human peripheral blood mononuclear cells (PBMCs) exposed to short-term simulated microgravity revealed core features of immune impairment. Comparative transcriptomics identified conserved features of immune dysfunction across simulated microgravity and spaceflight, including changes in pathways linked to cytoskeleton dynamics, pyroptosis, temperature shock, proteostasis, nuclear receptors, interferon, interleukin-6 (IL-6) and sirtuin cascades.

Liquid biopsies—an alternative to traditional biopsies—extract cell-free nucleic acids from the blood or urine[36,37], which emerge upon space-relevant stress[38], ageing[39], metabolic disorders[40], inflammation[41], DNA damage and clonal mutations[42,43]. These can detect changes earlier than protein biomarkers[44], providing enhanced resolution of molecular heterogeneity compared with standard tissue biopsies[45]. Full-body molecular profiling using cell-free DNA (cfDNA) and cell-free RNA (cfRNA) from liquid biopsies, coupled with clonal haematopoiesis mutation scans[43,46], is a contemporary approach to mapping effects of spaceflight that is ongoing in astronauts under the SOMA protocol (Table 3).

The JAXA Cell-Free Epigenome (CFE) Study[47] conducted an 11-timepoint liquid biopsy study with 6 astronauts who stayed on the ISS for more than 120 days. The study showed that cfRNA in plasma can capture longitudinal gene expression profiles of stressed or lysed internal tissues. The cfRNA analysis before, during and after spaceflight also revealed mitochondrial dysregulation in space[36], supporting previous studies[13,48,49]. The cfDNA analysis revealed a significant increase in relative mitochondrial DNA copy numbers during spaceflight, returning to baseline post-flight[36], replicating findings from the NASA Twins Study[13]. The association of the extracellular mitochondria (exMT)-enriched fraction with the CD36 scavenger receptor and the release of exMT-containing extracellular vesicles into the plasma during spaceflight indicated systemic metabolic stress responses to the space environment. These results suggest exMT as a potential biomarker to assess tissue responses in spaceflight and to interrogate tissues undergoing apoptosis, and reinforce theories that mitochondrial dysregulation is a central feature that increases health risks associated with spaceflight.

Mitochondrial and immune function are interconnected and affect insulin and oestrogen signalling, and pose increased health risks for the female reproductive system[50]. An integrated analysis of mouse, JAXA cfRNA, and I4 scRNA-seq data revealed altered mRNA levels during and after spaceflight, affecting mitochondrial metabolic pathways, particularly lipid metabolism and oxidative stress[4]. These changes contribute to increased health risks associated with reproductive hormone synthesis. Mitochondrial dysfunction in response to spaceflight was further supported by a comprehensive multi-omics analysis of specimens from the I4 crew[3,30]. Distinct alterations in macrophages, neutrophils and $CD4^+$ T cells, along with increased levels of IL-6, were detected in the scRNA-seq data, suggesting their potential effect on mitochondrial regulation, even in the relatively short I4 mission.

Organ and tissue responses in spaceflight

The cellular changes that occur during spaceflight illustrate a consistent story of immune perturbation, DNA damage and mitochondrial stress, evidenced across cellular, model organism and human astronaut models. Given the widespread cellular and molecular changes, studies have examined the combined effect of spaceflight at the organ and tissue levels. Here we will highlight the studies utilizing both existing data from model organism studies and astronaut data from the Twins Study, I4 and JAXA missions.

Muscle health is a crucial aspect of space research[19], given the abnormal changes undergone by this tissue during extended space missions, involving microgravity and radiation exposure. These changes can result in muscle mass decline and bone density loss, posing challenges for astronauts' recovery upon returning to Earth and potentially accelerating biological decline or frailty[47]. These issues mirror sarcopaenia, which is characterized by muscle loss and frailty and often observed in older adults, and current countermeasures are relatively ineffective[51]. Castañeda et al.[52] identified key genes associated with sarcopaenia and found these genes to be dysregulated when comparing human cells sent to the ISS and astronaut data from the JAXA and I4 missions. Notably, expression profiling in skin from I4 astronauts revealed deregulation of genes related to muscle loss, suggesting that skin data could serve as informative indicators of muscle-related gene deregulation[53]. The study further predicted potential countermeasure drugs targeting sarcopaenia-associated genes[52].

In an additional study addressing muscle loss, Kamal et al.[54] developed a microgravity bioreactor using the StrexCell system to release a daily bout of uniaxial cyclic stretch, which elicits changes in tensile loading on skeletal muscle myotubes. They provided evidence that this uniaxial bioreactor for skeletal muscle loading and unloading could be used for the study of mechanotransduction in skeletal muscle during future spaceflight. The StrexCell bioreactor system could also be used to test countermeasure strategies against the adverse effects of microgravity and could also help in studies of ageing[55].

Skin-related issues such as inflammation and discomfort during spaceflight are well-known, but molecular insights and mitigation strategies are limited. Two manuscripts in this package enhance our understanding of skin changes during long- and short-duration spaceflight, and feature the first astronaut skin biopsies. Cope et al.[56] conducted a comprehensive analysis using transcriptomic skin data from OSDR, correlated mouse and astronaut data from various missions, and identified responsive pathways in cell cycle regulation, lipogenesis, DNA damage and mitochondrial dysregulation. In a second study, Park et al.[57] analysed 3-mm human skin biopsies before and after spaceflight, revealing metabolic changes, DNA repair, cell cycle alterations and immune system activation. Inflammatory responses and immune deregulation, driven by KRAS, were observed across skin tissue layers, consistent with cellular responses in previous studies.

Beyond muscle and skin, studies have delved into molecular changes affecting the central nervous system (CNS) and neuronal tissues, caused by exposure to GCR and microgravity. Desai et al.[58] simulated acute and chronic GCR exposure in mouse models, and observed differences in psychomotor vigilance. The study highlighted potential adverse effects on attentional processes and reaction time, emphasizing the importance of cognitive and neurological metrics for in-flight mission decision-making. The investigation also explored the link between GCR exposure effects on neurocognitive performance and neurotransmitter abnormalities affecting circuit connectivity. Chronic GCR exposure was found to increase levels of neurotransmitters within the prefrontal cortex, indicating potential interventions targeting dopamine pathways to restore homeostatic signalling in the irradiated brain.

Masarapu et al.[59] and Houerbi et al.[60] examined brain alterations in ISS and ground control mouse models using spatial transcriptomics and single-cell multi-omics (RNA-seq and assay for transposase-accessible chromatin with sequencing (ATAC-seq)). These studies provided evidence of spaceflight-induced disruptions in neurogenesis, neuronal development, synaptogenesis and neurodegeneration that bear similarities to changes observed in ageing and neurodegenerative diseases. Spatial transcriptomic data suggested a disrupted blood–brain barrier

Table 3 | Study design and biospecimen collection schemes for current omics-based flight studies

		Assays and purpose		
	Protocol	**NASA HRP core measures**	**Baylor/TRISH omics**	**SOMA**
Blood	Whole blood	-	CLIA WGS and pharmacogenomics	CLIA WGS and pharmacogenomics
		Blood cell count (CBC)	Blood cell count (CBC)	Blood cell count (CBC)
		Metabolic panel (CMP)	Metabolic panel (CMP)	Metabolic panel (CMP)
	Serum	Biochemistry (JSC panel)	Biochemistry (JSC panel)	Biochemistry (JSC panel)
	Plasma	Proteomics (and glycoproteomics)	Proteomics	Proteomics (untargeted and targeted)
		Lipidomics	-	Lipidomics
		Metabolomics	Metabolomics	Metabolomics
		-	-	Exosome or EVP profiles and proteins
	PBMCs	-	-	Viably frozen cells (in DMSO)
		-	-	Telomere length
		-	-	Clonal haematopoiesis panel
		-	scRNA-seq	snRNA-seq
		-	-	scATAC-seq
		Functional immune assessment	Immune profiling	Single-cell BCR and TCR sequencing
	cfDNA	-	-	cfDNA sequencing
	cfRNA	-	-	cfRNA sequencing
	PAXgene RNA	RNA-seq	RNA-seq	polyA RNA-seq and ribo-RNA-seq
		-	-	Direct RNA-seq
Cheek epithelia	Buccal swab	WGS	-	Metagenome and metatranscriptome sequencing
		-	-	Metabolomics
Urine	24-h void	Proteomics	-	Proteomics
		Lipidomics	-	Lipidomics
		Metabolomics	-	Metabolomics
		Biochemistry (JSC panel)	-	Biochemistry (JSC panel)
	Morning void	-	Dipstick	Dipstick
		-	16S	Metagenomics
		-	-	Proteomics
		-	Metabolomics	Metabolomics
		-	-	Exosomes
		-	-	cfDNA and cfRNA sequencing
		-	-	Biochemistry (JSC panel)
Saliva 1-day	Crude saliva	Immune and qPCR viral panel	-	Immune and JSC qPCR viral panel
	Oragene	WGBS	16S	Metagenome and metatranscriptome sequencing
Microbiome	Body swabs	Metagenome	16S	Metagenome and metatranscriptome sequencing
	Saliva	Metagenome	16S	Metagenome and metatranscriptome sequencing
	Faecal	Metagenome	16S	Metagenome and metatranscriptome sequencing
	Vaginal	-	-	Metagenome and metatranscriptome sequencing
Spacecraft	Swabs	-	-	Environmental data
		-	-	Metagenome and metatranscriptome sequencing
Hair follicles	Hair	-	-	Telomere length
		-	-	Nucleic acid banking
		-	-	Metagenome and metatranscriptome sequencing
Semen	Sperm	-	-	Concentration, size, count, motility and morphology
Skin biopsy	3-mm punch	-	-	Spatial transcriptome and proteome
		-	-	Histology and morphology

A comparison of data generated as part of the NASA Human Research Program (HRP) Spaceflight Standard Measures and Omics Archive studies, Translational Research Institute for Space Health (TRISH) efforts, and SOMA. Data-generation protocols include WGS in Clinical Laboratory Improvement Act (CLIA) laboratories, pharmacogenomics, whole-genome bisulfite sequencing (WGBS), complete blood counts (CBC) with differential, complete metabolite panel (CMP), biochemical assays with the Johnson Space Center (JSC) panel, extracellular vesicles and particles (EVPs), and B cell receptor (BCR) and T cell receptor (TCR) repertoires. Some variations include glycoproteomics or polyadenylated (polyA) and ribosomal RNA-depleted (ribo-) RNA-seq. Most samples are aliquoted and banked into long-term archives, including viably frozen cells in dimethyl sulfoxide (DMSO). qPCR, quantitative PCR; scATAC-seq, single-cell assay for transposase-accessible chromatin with sequencing.

in rodents during flight, underscoring the importance of continued monitoring for brain health in future crews.

Cardiovascular tissues and related organs are also severely affected by the space environment and subject to increased health risks. Paar et al.[61] investigated the effect of space radiation on the heart, focusing on GCR-induced cardiac fibrosis. Activation of fibrosis-associated genes and pathways, including TGFβ1, was observed in blood samples from I4 and JAXA CFE Study astronauts. Simulated GCR experiments in mice revealed time-dependent regulation of fibrotic processes, indicating the potential for developing novel countermeasures targeting various fibrotic markers related to spaceflight response. The study explored the influence of circulating miRNAs linked to spaceflight-associated cardiovascular risks[61,62], and tested engineered miRNA-silencing oligonucleotides (antagomirs) targeting miR-16-5p, miR-125b-5p and let-7a-5p to mitigate cardiac fibrosis. The treatment restored TGFβ1 and type I collagen signalling to control levels, highlighting the potential for developing novel countermeasures.

The kidney—which is often understudied in spaceflight—was the focus of a comprehensive study by Siew et al.[63]. The I4 crew members exhibited changes in urinary chemistry during spaceflight that were associated with primary alterations in ion transporter regulation. Diverse approaches, including morphometry, imaging and multi-omics on rodent kidneys from the ISS, simulated ground analogue experiments as well as the I4 data revealed functional and structural renal remodelling in spaceflight. Acute GCR exposure reulted in increased expression of markers of mitochondrial distress and early proteinuria, suggesting glomerular and proximal tubule dysfunction. These findings suggest the possibility of transient, maladaptive nephron remodelling that might lead to progressive kidney damage during long-duration deep space missions, underscoring the importance of appropriate mitigation strategies.

Recognizing the radiosensitivity of each tissue and organ is crucial for targeted research and countermeasures. Radiosensitive organs, including haematopoiesis-related organs, reproductive systems, gastrointestinal system, epidermis and eyes, exhibit the greatest sensitivity to—and risk from—space radiation[64]. As deep space missions become more feasible, understanding and mitigating the risks posed by constant exposure to low-dose space radiation becomes imperative. Mitochondrial exhaustion due to inflammation and immune suppression[64] becomes a concern, particularly for organs that are less sensitive to radiation, such as the brain and muscles, which also require monitoring in spaceflight.

Systemic effects of spaceflight

With a better understanding of how the space environment affects humans at the cellular, organ and tissue levels, the overall biological response at the whole-body, host–microbial and systemic levels can be better understood and linked to prior work[19]. For example, understanding how spaceflight can advance ageing and affect overall frailty can leverage a wide range of studies and indicate a systemic change. Camera et al.[51] focused on establishing a frailty index for humans during spaceflight that links to well-defined hallmarks of ageing[39,51,65], including mitochondrial dysfunction, telomere alterations, genomic instability, epigenetic alterations, loss of proteostasis, deregulated nutrient sensing, cellular senescence, stem cell exhaustion and altered intercellular communication. Studies in this package link some aspects of spaceflight to the hallmarks of ageing pathology, indicating signs of premature ageing for some missions. The systemic effects can contribute to advanced muscle loss or sarcopaenia, cardiovascular health risks (such as fibrosis), clonal haematopoiesis, immune dysfunction, CNS issues, and other health issues. Camera et al.[51] created the frailty index using data from the OSDR (https://osdr.nasa.gov/bio/) from missions with mice and cell cultures that were flown to the ISS, simulated human microgravity experiments (bedrest studies[66]) and astronaut data from the JAXA study and I4 mission. Camera et al.[51] focus mainly on the effects of frailty on muscle tissue, which revealed a key set of genes associated with an early frailty phenotype. Specifically, they observed key changes in the interferon inflammatory response, metabolic disorders, hypoxia response and increased cellular senescence.

The I4 mission provided a vast amount of physiological and molecular data from the four civilian astronauts, spanning the six research projects, thousands of samples and three mission phases[7] (Table 3). Key measurements include multi-omics and virome analysis associated with spaceflight, organ ultrasound imaging (ButterflyiQ+) and comprehensive cardiovascular and neurocognitive assessments. Systemic alterations were evident post-flight, particularly in human PBMCs, showing thousands of differentially expressed genes at one day after return to Earth (that is, R + 1). Notably, $CD14^+$ and $CD16^+$ monocytes exhibited the most significant changes in gene expression, which were linked to regions of more open chromatin, including genes associated with DNA repair, immune activation and nucleosome organization[8]. Physiological changes were recorded using handheld ultrasound devices for autonomous imaging of the urinary bladder, internal jugular vein and eyes. Generally, short-duration spaceflight did not induce significant physiologic changes post-flight relative to pre-flight. However, crew members, even those who did not exhibit space motion sickness, exhibited consistent vertical ocular misalignment post-flight, contrasting with pre-flight conditions. Cardiovascular function, activity levels, and energy expenditure were measured using the Apple Watch series 6, marking its inaugural use in spaceflight. Neurocognitive performance was assayed using a battery of ten cognitive tests developed for astronauts that has been deployed in both spaceflight and ground-based spaceflight analogue studies.

Although the effects of short-duration spaceflight on cardiovascular function and neurocognitive performance were modest, there were marked interindividual differences in response to spaceflight, consistent with previous research[67,68]. Significant changes in heart rate, heart rate variability, energy expenditure and activity levels occurred across mission phases. Furthermore, the spacecraft environment can affect crew physiology and neurobehavioural functions[68] and three out of the four I4 crew members exhibited positive associations between CO_2 levels and heart rate variability in flight. Moreover, cfRNA and cfDNA profiles revealed that cells with the greatest rate of lysis were from the haematopoietic system[8,60], mirroring the radiation risk of this system. Overall, the findings from the orbital mission demonstrate that the collection of high-quality biomedical and behavioural data is feasible in a commercial crew with rapid training, and how systemic and whole-body level analysis from omics and biometrics data generates rich profiles describing the effect of spaceflight on the human body.

During spaceflight, alterations in host–microbial interactions have a systemic effect, particularly as microorganisms adapt to novel and extreme environments by incorporating new genetic material, particularly through bacteriophages[69]. Bacteriophages, upon inserting viral DNA into hosts, can become dormant (prophages), leading to modified host genotypes with gene disruption[70], silencing and chromosomal rearrangement, thereby influencing host gene expression[8]. Prophages facilitate the transfer of bacterial genes, including virulence and antibiotic resistance genes, toxins, effector proteins and regulatory proteins, among cells[71]. Irby et al.[72] investigated prophage presence and function in the genomes of bacteria isolated from the ISS compared with terrestrial counterparts, exploring their contribution to microbial adaptation in the spaceflight-built environment. Analysing ten bacterial species from five ISS sampling campaigns, they identified significant spaceflight-related differences in mobile genetic elements, particularly prophages. Whereas transposes are common in terrestrial strains, they are notably absent in ISS strains. Instead, ISS strains exhibit an increased prevalence of Mu-like and unclassified phages. This variation suggests that selective pressures unique to the space environment, such as limited nutrient availability and heightened

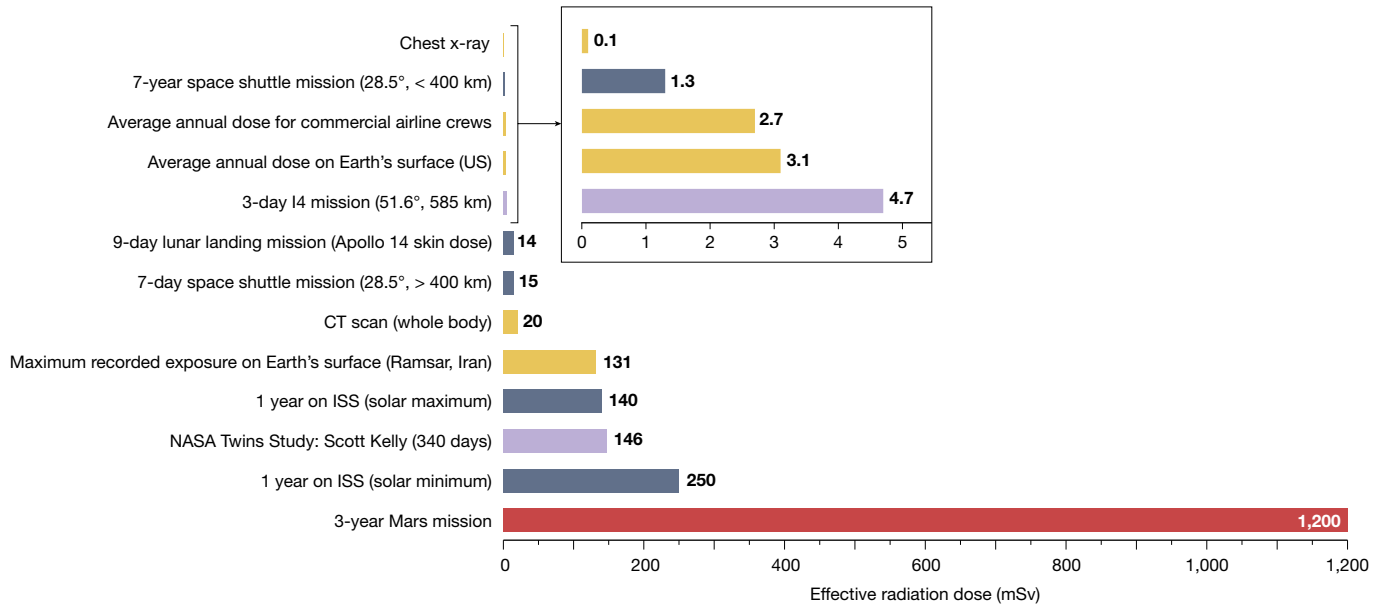

Fig. 2 | Radiation levels of the I4 mission, NASA Twins Study and other exposures. Yellow bars denote the low linear energy transfer (LET) radiation (or terrestrial radiation). Purple bars denote the radiation levels experienced during the Inspiration4 mission and Scott Kelly year-long mission (NASA's Twins Study). The red bar depicts the estimated radiation dose of a future three-year mission to Mars. Blue bars denote all other high LET radiation doses.

genetic diversity, promote microbial survival under these conditions. Overall, the study indicated that prophage-encoded functions correlated with increased microbial persistence on the ISS, providing insights into potential mechanisms for microbial adaptation to this unique environment.

The I4 mission also created the largest astronaut microbiome study to date[73], spanning 750 samples across 10 time points, with shotgun metagenomics and metatranscriptomics performed for each sample. These data showed a microbiome architecture of spaceflight that was characterized by time-dependent and taxonomically divergent microbiome alterations across both time and space (including strain exchange with the SpaceX Dragon spacecraft). They also observed pan-phyletic viral activation and signs of persistent changes that—in the oral microbiome—yielded plaque-associated species with strong associations with immune cell gene expression. Further, they found enrichments of microbial genes associated with antibiotic production, toxin–antitoxin systems and stress response enriched universally across the body sites, and were correlated with some of the T cell and B cell expression dynamics in the crew.

Countermeasure development for spaceflight

There are limited medical countermeasure options specifically designed to decrease the negative effects of radiation exposure in astronauts due to spaceflight. Currently, there are three such countermeasures that have been approved by the US Food and Drug Administration (FDA): Neupogen (filgrastim), Neulasta (pegfilgrastim) and Leukine (sargramostim), which are intended to improve survival following exposure to an acute myelosuppressive radiation dose[74]. These countermeasures improve the likelihood of survival by mitigating neutropaenia and thrombocytopaenia associated with acute radiation sickness. However, their effectiveness has been studied primarily in the context of photon irradiation, with limited evaluations for proton or other radiation qualities experienced during spaceflight, such as GCR. Additionally, although the FDA-approved radioprotectant Ethyol (amifostine) is available to reduce xerostomia post-radiotherapy for head and neck cancers, its utility in mitigating the effects of space radiation is limited owing to its parenteral administration, short half-life and side-effects.

Addressing the challenges posed by space radiation and microgravity, Paar et al.[61] explored the potential of miRNA inhibitors as a countermeasure. They tested the ability of inhibitors targeting specific miRNAs (miR-16-5p, miR-125b-5p and let-7a-5p) to alleviate cardiac fibrosis in mice exposed to simulated space radiation and microgravity. A complementary study by McDonald et al.[62] identified these miRNAs based on a previously established circulating miRNA signature associated with the space environment[75]. Using a 3D human model for microvessel physiology, inhibition of these miRNAs demonstrated significant preservation of the human microvessel structure, reducing DNA damage and stress after exposure to simulated GCR. This approach, supported by observations in both 3D human microvasculature tissue model and astronaut data from missions such as JAXA and I4, indicates the potential effectiveness of miRNA inhibitors in countering specific challenges encountered during spaceflight.

Expanding countermeasures to address skin-related issues observed in various datasets, including spatial transcriptomics from the I4 mission, JAXA CFE and mouse models[56], offers insights into potential interventions. Altered expression of *FLG* and *CASP14*, genes known to modulate skin permeability, during and after flight indicate that these genes may be involved in water loss and responses to irritants, allergens and microbial products during spaceflight. *FLG* loss-of-function mutations are associated with conditions such as atopic dermatitis. This can be treated by dupilumab, which inhibits interleukins 4 and 13, and thereby upregulates *FLG* expression and restores epidermal barrier function. This drug could be explored for in-flight and post-flight treatment to restore skin barrier function[76].

Of note, miRNA-based countermeasures offer innovative potential to mitigate space radiation damage; however, extensive pre-clinical and clinical trials are essential before human implementation. Meanwhile, repurposed drugs are being explored as countermeasures for spaceflight-related damage, particularly addressing symptoms from solar particle events[77]. Anti-nausea medications such as ondansetron, granisetron, palonosetron, Imodium (loperamide), Neupogen, corticosteroid cream and dolasetron are considered for mitigating symptoms from solar particle events (for example, nausea, vomiting, diarrhea, radiation dermatitis or neutropaenia). Flavonoid supplements (such as apigenin[78]) and vitamin D[79], along with exercise[80] have also been investigated as countermeasures to reduce inflammation[81]

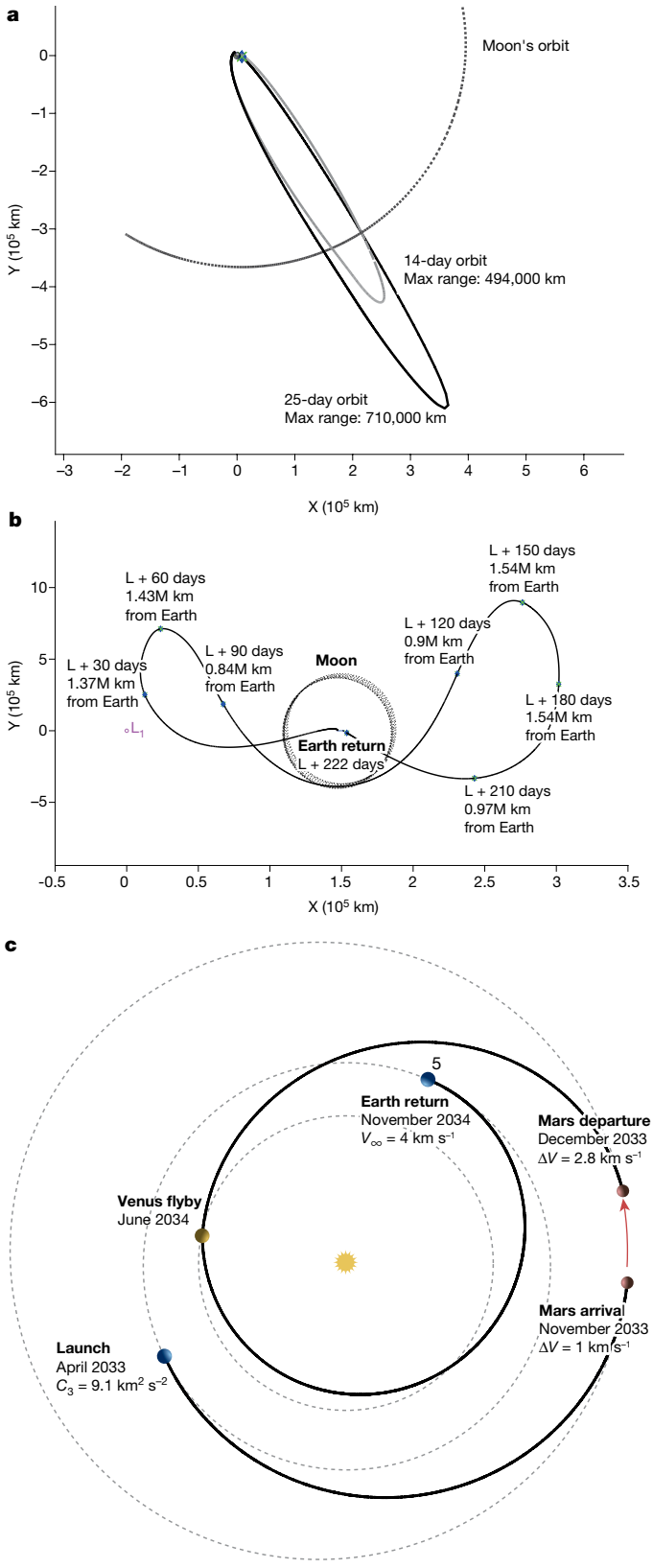

Fig. 3 | Long-duration missions enabled by heavy-lift rockets. a, The orbital trajectory and future missions enabled by the current Dragon capsule parameters. **b**, Extra-lunar orbital trajectory that would approach the Lagrange point 1 (L1) closer to the sun and up to 1.54 million kilometres from the Earth (central blue diamond). The moon's orbit is shown as a dotted line around the Earth. **c**, The orbital trajectory for a three-planet mission in 2033 that would fly past Mars twice and past Venus within about 18 months. The launch date and approximate timings are shown around the planetary orbits (dashed circles) and the flight path (solid). The sun is shown in the middle of the panel. C_3 is the characteristic energy of the proposed launch.

and mitigate spaceflight damage. Until specific miRNA-based treatments are developed, a combination of FDA-approved drugs, nutritional supplements and microbial interventions[82] may be explored for comprehensive mitigation of spaceflight-induced damage.

Astronaut precision medicine (APM) emerges as an actionable countermeasure involving tailoring treatment and prevention to individual characteristics, encompassing molecular, physiological, morphological and behavioural aspects[83,84]. Pharmacogenomics, a cornerstone of APM, examines gene variants that influence drug metabolism[85,86] to optimize drug safety and efficacy for individual astronauts. Developing pharmacogenomics profiles of astronauts and crews could ensure personalized drug regimens, enhancing mission safety and effectiveness.

This principle can be applied to many of the drugs in a mission formulary. Crucially, these types of drug responses can be predicted and personalized. The application of pharmacogenomics (drug–gene interactions) should also be accompanied by careful attention to drug–drug, drug–nutrient, drug–food, drug–microorganism and drug–herb interactions. These can be systematically assessed for individuals and crews and can be implemented using large cohort databases and routine sequencing for the crews. Addressing these interactions removes another potential impediment to astronaut health, safety and performance.

Applying APM and pharmacogenomics to space missions involves molecular phenotyping to characterize functionally related molecular networks[83]. By addressing dysregulations before space missions, APM aims to prevent their effect on health, safety, and performance in the space environment. Targeting specific substances produced by gut microorganisms, such as the increased neurotoxin and nephrotoxin *p*-cresol observed in the NASA Twins Study[87], enables dietary countermeasures, including fibre and resistant starch, to lower *p*-cresol production. APM may also address challenges such as space-associated neuro-ocular syndrome by characterizing genotypes and metabolites related to the one-carbon molecular network.

Beyond the pharmacological and physical countermeasures, genetic and epigenetic tools have emerged as innovative approaches to mitigate spaceflight-associated risks. CRISPR technologies, utilizing Cas9 and other Cas systems, enables precise modification of somatic cells to correct or replace disease-driving genes. Specifically, recent clinical trials have successfully treated conditions such as beta-thalassaemia and sickle-cell disease by deleting repressor genes for fetal haemoglobin[88]. Epigenetic modification systems that utilize deactivated Cas9[89] (dCas9) fused with histone or DNA modifiers such as DNMT3A or TET1 enable targeted modification of gene expression, providing a means for permanent or transient genetic alterations related to spaceflight. These advancements may have a crucial role in addressing long-term challenges for human settlement on other planets[90].

Computational and omics tools

Advanced computational methods, omics platforms and new algorithms play a pivotal part in understanding factors related to spaceflight health. Casaletto et al.[91] utilized machine learning techniques, specifically the Causal Research and Inference Search Platform (CRISP), to predict features causally linked to a binary response variable, employing prediction invariance as a guiding principle. By applying CRISP to gene expression data from OSDR, they identified genes and molecular targets associated with lipid density phenotype in space-flown rodents. This approach unveiled novel insights not captured by traditional systems biology methods, particularly in addressing liver dysfunction. The SOMA resource paper[8] also features four data portals and tutorials on

data usage, to help further discovery and replication across missions. The study highlights the importance of a causal inference framework based on environment invariance for robust feature identification, emphasizing its applicability to various tissues, phenotypes and omics data. Continued advancements in computational and biological tools are crucial for comprehending the effects of spaceflight on health and developing effective countermeasures.

Limitations associated with space research

Although the NASA Twins Study[13] marked a significant stride in clinical genomics and multi-omics analysis during spaceflight, limitations on crew size and follow-up were evident. The I4 and JAXA studies, with $n = 4$ for I4, $n = 6$ for JAXA and $n = 14$ for an ISS astronaut study on bone marrow[92], have expanded the subject pool but still face constraints, especially when considering sex-specific analyses. The inherent challenges of limited numbers of human subjects in space experiments persist owing to constrained flight opportunities, regulatory restrictions and cost considerations.

Notwithstanding these challenges, meticulous planning, procedures and analysis, coupled with a skilled team, have demonstrated the generation of valuable insights from I4 and JAXA studies. Ground-based studies and control cohorts, including those such as HI-SEAS and analogue astronauts in EXPAND, alongside collaborations with initiatives such as the UK Biobank and commercial entities such as Pheno.AI and the Human Phenome Project, continue to enhance our understanding despite the inherent limitations in human subject numbers for space research.

Outlook

Although data from the various missions, computational tools, and model organisms provide valuable insights into the impacts of spaceflight, significant challenges persist. Some molecular signatures are consistent across both short and long-term missions (for example, increase in plasma IL-6 and IL-10, telomere elongation and mitochondrial stress), whereas others appear to be specific to extended exposure and chronic space radiation (for example, C-reactive protein spikes). The increasing radiation burden observed in missions such as I4 and future missions (Fig. 2) highlights the necessity for precision medicine strategies tailored to individual astronauts, ensuring the right treatment is available at the right time for the specific mission.

Previous work has identified mitochondrial dysfunction as a key driver of systemic damage during spaceflight[48], including inflammation, immune suppression, cardiovascular dysfunction, muscle atrophy, bone loss and circadian rhythm disruption. Whereas these systemic stresses appear universal, individuals experience varying degrees of dysregulation, necessitating astronaut-specific precision medicine to ensure safe space travel for all. Data from I4 and JAXA missions reveal both universal changes (increased inflammation and mitochondrial stress), independent of sex and ethnicity, and sex-specific variations (insulin and oestrogen changes in women)[4,8,33]. By aggregating these findings, we can identify systemic changes and construct a molecular fingerprint of key alterations, underscoring the importance of personalized healthcare for astronauts.

Although conventional countermeasures focus primarily on pharmacological interventions, emerging approaches utilizing RNA biology, omics-based methods and gene therapies offer promising avenues for active defence[93–95]. These advancements, coupled with genomic tools and personalized activation of specific alleles[88], have the potential to address individual health challenges encountered in space. However, careful consideration must be given to ethical concerns such as informed consent[96], crew ownership of data[97–99] and adherence to full Institutional Review Board (IRB) protocols as research in this evolving landscape progresses, especially for long-duration missions (Fig. 3), as well as for ground-based studies.

Indeed, ground-based analogue studies continue to complement spaceflight experiments[100–107], providing valuable insights into human responses to the space environment. As space research advances, integrating data from individuals of diverse ages, sexes and lifestyles is essential to facilitate a comprehensive understanding of genetic and epigenetic associations with space adaptation. Efficient subject stratification will be crucial for the successful evaluation of future medical interventions.

The data and new discoveries described above are exciting, but beg the question; how we will know when we have reached the end of the second space age? This could happen within a matter of decades. China and the USA have both announced plans for crewed missions to Mars (no earlier than 2035 and 2039, respectively), as well as for active work to return samples from Mars (Table 1). New trajectories enabled by heavy-lift rockets such as the Starship can enable missions that span longer lunar arcs (Fig. 3b) or three planets in one trip[108] (Fig. 3c), and future missions will be enabled by the current SpaceX Dragon parameters for crew and resources (Fig. 3a), enabling humans to travel further than they have before[109]. When successful, these events will signal the shift of humanity from a LEO-focused species to an interplanetary one, with instruments, missions and crews moving around the planets of our first solar system. Indeed, by 2050, there are likely to be: (1) orbital satellites around all planets in our Solar System (Table 1); (2) a permanent presence of humans on the Moon; (3) the first crewed visit to another planet (Mars); (4) exchange of materials and samples between planets; and (5) plans to send probes to other stars. When that celestial stage is set, we will enter the next space age, in which humans will be permanent travellers and explorers in space.

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