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Pharmacological countermeasures for long-duration space missions: addressing cardiovascular challenges and advancing space-adapted healthcare

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ABSTRACT

Future long-duration crewed space missions beyond Low Earth Orbit (LEO) will bring new healthcare challenges for astronauts for which pharmacological countermeasures (pharmacological countermeasures) are crucial. This paper highlights current pharmacological countermeasures challenges described in the ESA SciSpacE Roadmap, with a focus on the cardiovascular system as a model to demonstrate the potential implication of the challenges and recommendations. New pharmacological approaches and procedures need to be adapted to spaceflight (spaceflight) conditions, including ethical and reglementary considerations. Potential strategies include combining pharmacological biomarkers such as pharmacogenomics with therapeutic drug monitoring, advancing microsampling techniques, and implementing a pharmacovigilance system to gain deep insights into pharmacokinetics/pharmacodynamics (PK/PD) spaceflight alteration on drug exposure. Emerging therapeutic approaches (such as long-term regimens) or manufacturing drugs in the space environment, can address specific issues related to drug storage and stability.

The integration of biobanks and innovative technologies like organoids and organ-on-a-chip, artificial intelligence (AI), including machine learning will further enhance PK modelling leading to personalized treatments. These innovative pharmaceutical tools will also enable reciprocal game-changing healthcare developments to be made on Earth as well as in space and are essential to ensure space explorers receive safe effective pharmaceutical care.

Abbreviations: **ACE**, Angiotensin-converting enzyme; **AI**, artificial intelligence; **ARBs**, Angiotensin receptor blockers; **AT1**, Angiotensin II type 1; **AT1R**, Angiotensin II type 1 receptor; **AUC**, Area under the curve; **BLEO**, Beyond Low Earth Orbit; **CYP**, Cytochrome; **DBS**, Dried blood Spot; **ISS**, International Space Station; **LEO**, Low Earth Orbit; **PCSK9**, Proprotein convertase subtilisin/kexin type 9; **PD**, Pharmacodynamics; **PK**, Pharmacokinetics; **siRNA**, Small interfering RNA; **TDM**, Therapeutic drug monitoring.

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1. Introduction

The human space flight program has entered a new era marked by an acceleration of human exploration, the democratization of space travel, and the aspirations of space agencies to establish permanent settlements on the Moon and ultimately, the human exploration of Mars. The realization of these new space activities requires addressing the acute and chronic adverse effects of space environments on human health (Fig. 1). Currently astronauts spend on average six months in Low Earth Orbit (LEO). In coming years, crewed missions with extended periods beyond LEO (BLEO) will last over three years without the possibility to promptly return to Earth or access to emergency medical care. Thereby increasing distance/time from medical assistance on Earth, are expected. This is particularly relevant for future missions to the Moon and Mars where the risk for cardiovascular diseases and mortality will be greater than during LEO missions (Norsk, 2020, Delp et al., 2016). The expected increase in cardiovascular diseases morbidity necessitates further study of cardiovascular risk during spaceflight and its mitigation for astronauts. Changes induced by spaceflight are termed physiological however for this paper we will use the term space-induced changes rather than physiological changes because reversibility is not clearly evidenced, and long-term pathological consequences have been demonstrated (Delp et al., 2016). It is noteworthy that space-induced changes in major physiological systems persist despite the implementation of physical and nutritional countermeasures.

Intergovernmental, national space agencies and private companies that organize long-duration spaceflight BLEO are required to ensure the health and safety of crews which includes providing safe, and effective pharmacological countermeasures. Space-induced changes may alter drug pharmacokinetics (PK, how the body handles the drug) and pharmacodynamics (PD, how the drug affects the body), mitigating their efficacy/safety balance. Consequently, the health and performance of astronauts, which are pivotal to mission success, will depend on effective pharmacological countermeasures, especially for long-duration BLEO missions. Given the multiplicity of the different sectors of pharmacology, and the extensive range of regional and national regulations, the term pharmacological countermeasures used in the present paper designates any type of pharmacotherapy or targeted therapeutic approach for health benefits (Boutouyrie et al., 2021). Previous literature reviews have highlighted a number of shortcomings in the understanding of PK/PD and pharmaceutical stability during spaceflight (Wotring, 2012). To address these gaps, a space pharmacological countermeasures Topical Team was established by the European Space Agency (ESA), whose objectives are to develop recommendations outlining research priorities for future space pharmacological research. The outcomes of this initiative are summarized in a publicly available roadmap (ESA SciSpace Roadmap) (Boutouyrie et al., 2021). The objectives of the present paper are to substantiate strategies for conducting space pharmacology studies for achieving a comprehensive understanding of pharmacological countermeasures. Those pharmacological countermeasures should be designed to preserve the operational efficiency of astronauts but also their future health. We thus propose a framework to develop effective treatments tailored for astronauts as individuals in the extreme conditions of space, Lunar, and Martian environments. Although all physiological systems are affected by space-induced changes, we chose the cardiovascular system as a case study. However, the scope of the review paper is broader, as the pharmacological countermeasures principles can be applied to any physiological system.

2. Differences between earth and space environment

2.1. Earth vs. space environment

During spaceflight, astronauts face stressors like microgravity, isolation, circadian rhythm changes and radiations including high energy particles produced from solar particle events, heavy ions contained in galactic cosmic rays (Chancellor et al., 2014) as primary radiations, and secondary radiations. Those stressors, when combined, cause significant space-induced body changes (Comstock et al., 1971, Fleischer et al., 1973). Microgravity leads to muscle atrophy, bone demineralization, cardiovascular, pulmonary, and renal dysfunctions, reduced immune competence, metabolic changes, and neuro-ocular alterations. Microgravity annihilates gravitational mechanical forces and body

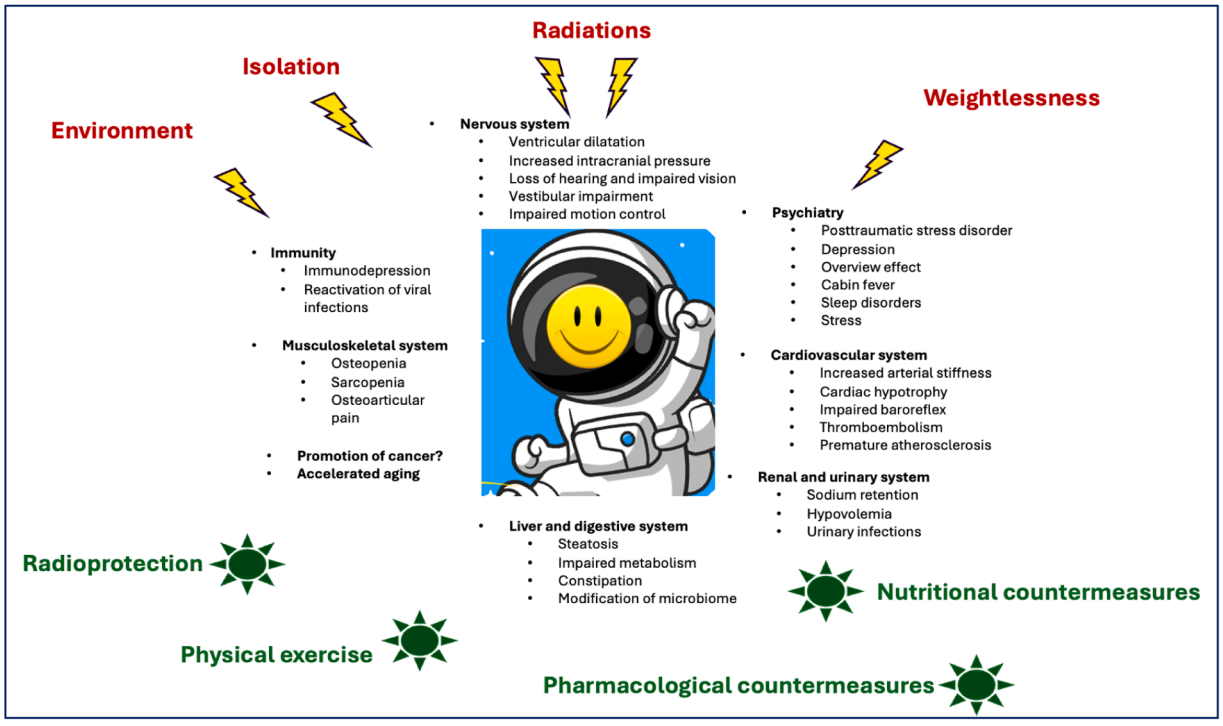

Fig. 1. Major threats associated with spaceflight, consequences on the body, and principal countermeasures.

motion forces against gravity which are strong signals for cytoskeleton and extracellular matrix remodeling. Besides, radiations and chemical stressors may affect the oxidative metabolism through mitochondrial and oxidative chain alterations. Forced inactivity in microgravity further contributes to these changes by muscle mass waste and lipid accumulation (Fig. 1).

These space conditions may promote cardiovascular diseases (Hughson, 2016). The Artemis lunar missions and Mars missions will expose crewmembers to increased galactic cosmic rays and likely high-intensity solar particle events in the absence of Earth's protective magnetic field. They will be further exposed to prolonged isolation in a confined environment with an evolving ecosystem and to additional hazards such as lunar dust, the component of lunar regolith, and dust storms on Mars (Afshinnekoo et al., 2020, James JT and Kahn-Mayberry, Patel et al., 2020, Miranda et al., 2023), altered gravity fields, variation in temperature and atmosphere in habitat and during extravehicular activities (despite controls). All these factors may impair the cardiovascular system. Interplanetary missions pose extra challenges due to the lack of immediate medical assistance with limited Earth contact and the transition to partial gravity environments after extended periods in microgravity or weightlessness.

2.2. Cardiovascular physiological effects: observed and expected

Space-induced changes that occur in the cardiovascular system during short-term spaceflight (<15 days) are well characterized, and result from the reductions in both the muscular exertion required to combat the force of gravity on Earth and the reliance on the lower body for locomotion. As hydrostatic pressure is alleviated in the lower limbs and interstitial sodium retention increases, overall blood flow to the muscles declines with subsequent decreases in cardiac output and hemodynamic load, and a resetting of baroreceptors (Norsk, 2020), which in turn can trigger the acute orthostatic intolerance frequently observed in astronauts returning to Earth (Fritsch et al., 1992) .

The cardiovascular modifications also increase the risk for longer-term cardiac and vascular changes. Thus reduced hemodynamic load results in structural remodeling of the cardiovascular system, with a decrease in cardiac volume and mass, and space-induced early vascular ageing and an increase in arterial stiffness similar to 20 years of aging for 6-months missions in LEO (Hughson, 2016, Hughson et al., 2018). The NASA Twins Study of 1-year mission revealed that carotid intima-media thickness increased dramatically after launch and remained thicker until 4 days after landing (Garrett-Bakelman et al., 2019). These modifications are likely to adversely impact the health of astronauts during long missions and after their return to Earth. The reversibility of this space-induced early vascular ageing is poorly studied and involves complex multifactorial mechanisms.

Extracellular matrix turnover is a constant physiological process characterized by matrix metalloprotease regulated activity, macrophage activation and dynamic changes in cell-cell and cell-matrix attachments (Lacolley et al., 2017). On Earth, extracellular matrix turnover is a particularly slow process and therefore the reversibility of space-induced changes of extracellular matrix remodeling is questionable for the cardiovascular system (Boutouyrie et al., 2022) and for bone (Vico et al., 2017) after return on Earth. It can, however, be much faster if the mechanical environment of tissues is acutely changed (Szafron et al., 2024) and hence cardiovascular space-induced changes occur rapidly during spaceflight (Szafron et al., 2024).

Thrombosis risks is increased in space in healthy astronauts. A study on 11 healthy crewmembers assigned to long-duration flights showed a sevenfold increase in internal jugular vein cross-section area, with stagnant or reverse flow observed in six crewmembers (Marshall-Goebel et al., 2019). An occlusive thrombus was found in one subject, and a partial thrombus in another (Auñón-Chancellor et al., 2020). The degree to which the space environment increases the risk of thromboses remains unclear. At least, it complicates management (Auñón-Chancellor et al., 2020). spaceflight also induces significant metabolic changes (Bergouignan et al., 2016), such as insulin resistance (Tobin et al., 2002, Hughson et al., 2018, Mathyk et al., 2024), dyslipidemia, and immune dysregulation, which could contribute to cardiovascular health risks during longer-term space missions (Hughson et al., 2018) .

Long-term spaceflight triggers inflammation, which in turn increases the risk of allergy or autoimmune disease (da Silveira et al., 2020). The spaceflight-induced pro-inflammatory state is characterized by an abnormal peripheral blood leukocyte count, elevated neutrophils, and significantly amplified TNF and IL-1β responses following fungal antigen stimulation. However, regulatory T cell, IL-1ra, IL-10 and TGF-β levels were all seen to drop post-flight (Buchheim et al., 2019) . Notably, space-induced immune system changes resemble those associated with the aging process, known as "inflammaging "(Hicks et al., 2023). Inflammation is a major external factor influencing early vascular aging (Zanoli et al., 2020).

Liver-related changes have been reported in ISS (International Space Station), microgravity ground-analog human (Rudwill et al., 2015) and animal models (Beheshti et al., 2019, Jonscher et al., 2016), with damage contributing to increased lipid and fatty acid processing, potentially leading to fibrosis and early onset of metabolic dysfunction-associated steatotic liver disease (da Silveira et al., 2020, Vinken). Increased cholesterol levels (both low and high-density lipoprotein) have been observed after 180 days spaceflight, with elevated levels persisting up to 30 days post-flight. Mitochondrial dysfunction (Silveira, 2020) and increased reactive oxygen species are likely contributors to these metabolic issues (Paradies et al., 2014).

The metabolic alterations observed in astronauts are reminiscent of those with chronic metabolic disorders such as type 2 diabetes, obesity, or metabolic syndrome. As a result, astronauts are at increased risk of developing these conditions early during their mission, and later. An under-evaluated problem in spaceflight is the impairment of wound healing due to both persistent oxidative stress and inflammation and metabolic changes. In these conditions, the wellness of the microcirculation and the ability to promote angiogenesis, crucial for proper tissue recovery, are blunted (Morbidelli et al., 2021).

2.3. Radiation

Radiations are one of the major stressors for humans in the space environment and given the increasing evidence of the long-term cardiovascular consequences of nuclear bomb irradiation (Takahashi et al., 2017) and radiation therapy for pediatric cancer one to which the cardiovascular system is known to be particularly sensitive (Belzile-Dugas and Eisenberg, 2021). Indeed, exposure to space radiation has been seen to aggravate spaceflight-induced cardiovascular lesions in the long term (Patel, 2020), and the potential additional effects of high energy galactic cosmic rays cannot be ignored. However, the long-term impact of these space-induced changes beyond the current mission durations (>1 year) remains largely unknown (Gao and Chilibeck, 2020). Furthermore, the hazards and associated cardiovascular risks evolve dynamically during space missions. Therefore, it is particularly important to develop and implement preventive pharmacological countermeasures capable of preventing or limiting spaceflight-induced cardiovascular changes to ensure the efficiency, safety and well-being of the crew.

2.4. Pharmacological strategies to prevent cardiovascular risks in long-duration spaceflights (Over 6 Months)

2.4.1. Repurposing cardiovascular-metabolic drugs to counteract space-induced early vascular ageing

On Earth, cardiovascular risk factors such as hypertension, diabetes and dyslipidemia can be effectively treated and even reversed by medication (Olawi et al., 2019, Savoia et al., 2021, Li et al., 2020, Ouslimani et al., 2005, Agarwal et al., 2010, Valencia et al., 2017, Tentolouris et al., 2019, Durante et al., 2021, Shigiyama et al., 2017,

Lambadiari et al., 2018, Scalzo et al., 2017, Janić et al., 2014, Liao and Laufs, 2005, de Almeida et al., 2020, Howard et al., 2021). Clinical experience—and notably terrestrial observations of early vascular aging (Barinda et al., 2024)—suggests that pharmacological countermeasures have the potential to prevent the onset of space-induced changes and to help recovery on return to Earth (Table 1).

Antihypertensive and lipid-lowering drugs are known to improve features of early vascular aging on Earth (Table 1) (Laurent et al., 2021, Boutouyrie et al., 2021). Selecting appropriate cardiovascular pharmacological countermeasures for space travel requires thorough characterization of drug pharmacology, including all PK determinants. Candidate pharmacological countermeasures should be assessed based on: (a) widest therapeutic range for the indication; (b) extent of renal and hepatic elimination; (c) effect of plasma protein binding on distribution and elimination. The ideal pharmacological countermeasures or combination of pharmacological countermeasures should be also cost-effective, easy to administer, and beyond their primary action, also have multiple positive effects, known as pleiotropic effects within the body without harming other bodily functions or eliciting serious adverse effects (Custaud et al., 2020). This is particularly the case with statins, whose preventive effect on cardiovascular complications is explained not only by the reduction of LDL cholesterol levels, the initial and probably essential objective, but also by multiple pleiotropic effects such as plaque stabilization, improvement of endothelial function, anti-inflammatory effect, or antioxidant activity (Liao and Laufs, 2005). Statins help manage cholesterol levels and prevent atherosclerosis, thereby reducing cardiovascular risk.

Table 1
Pharmaceutical preparations with known effects on cardiovascular remodeling, and their potential as pharmacological countermeasures during space flight.

Drug class	Mechanism of action	Threats for space flight	How to minimize threats
Vasodilating beta-blockers (Olawi et al., 2019)	Reduce blood pressure and heart rate Antioxidant properties Improve endothelial function	Fatigue, excessive reduction in blood pressure and heart rate	Preflight testing
Angiotensin 2 antagonists (ARBs), angiotensin converting enzyme inhibitors (ACEi) (Savoia et al., 2021)	Antifibrotic, antioxidant, vasodilatory, decrease arterial stiffness	Low blood pressure, allergies (ACEi)	Prefer ARBs over ACEi
Thiazide diuretics (Li et al., 2020)	Negative sodium balance, reduce hypercalciuria, reduce bone demineralisation	Low blood pressure, low potassium	Potassium supplementation
Metformin (Ouslimani et al., 2005, Agarwal et al., 2010, Valencia et al., 2017)	Improve sensitivity to insulin, antioxidant, antiaging, improve oxidative metabolism, vasculoprotective	Lactatemia, Vit B12 malabsorption	Preflight testing Administration after meals
Glifozins (SGLT2 inhibitors) (Ouslimani et al., 2005, Agarwal et al., 2010, Valencia et al., 2017, Tentolouris et al., 2019, Durante et al., 2021, Shigiyama et al., 2017, Sugiyama et al., 2018)	Negative sodium balance, improve energetic metabolism, cardioprotective, decrease arterial stiffness Improve endothelial function	Increased urinary glucose excretion, risk of urinary infections, risk of ketosis	Low risk in normoglycemic subjects Urinary testing for nitrates
Glucagon-like Peptide (GLP)-1 agonists (Lambadiari et al., 2018, Scalzo et al., 2017)	Increase insulin secretion and decrease glucagon secretion	Risk of hypoglycemia on treatment initiation Pancreatitis	Preflight testing
Statins (Janić et al., 2014, Liao and Laufs, 2005)	Beneficial effects on endothelial function, reduce arterial stiffness	Myalgia though mainly nocebo driven (de Almeida et al., 2020)	Preflight testing Improved hydration and ion balance

Spaceflight-associated insulin resistance could be targeted. This condition is attributed to metabolic changes resulting from muscle atrophy due to reduced physical activity in microgravity. Insulin resistance is typically assessed using the Homeostatic Model Assessment for Insulin Resistance (HOMA-IR), which requires measurements of both insulin and glucose levels. While glucose can be easily monitored aboard spacecrafts, measuring insulin levels presents challenges and has not been reported during missions. Waist circumference, a simple measure often underreported in studies, could serve as a proxy for insulin resistance. Reported insulin resistance levels in astronauts range from mild to moderate. Given that astronauts already engage in regular exercise and maintain a balanced diet, these interventions cannot be further intensified. Initial therapeutic approaches should focus on enhancing insulin sensitivity using medications like metformin, PPAR-gamma agonists or Glucagon-like peptide 1 agonists, rather than administering insulin.

Beta-blockers, such as metoprolol and propranolol, can be used to manage heart rate and reduce the risk of arrhythmias that might arise due to the cardiovascular deconditioning in microgravity. Angiotensin-converting enzyme (ACE) inhibitors like enalapril and angiotensin 2 receptor blockers (ARBs) like irbesartan, help to manage blood pressure and reduce the risk of heart failure by relaxing blood vessels and reducing blood volume, with documented antifibrotic and blood pressure-independent destiffening effect on large vessels (Boutouyrie et al., 2021). Anticoagulants used to prevent blood clot formation, which is a risk in the microgravity environment, such as warfarin or direct oral anticoagulants (DOACs) like apixaban and rivaroxaban, may be used. Diuretics like furosemide may be used to manage fluid retention and blood pressure by promoting the excretion of water and salts from the body.

Calcium channel blockers like amlodipine can be used to manage blood pressure and reduce the workload on the heart by relaxing blood vessels. Antioxidants (such as Vitamin C and E) and anti-inflammatory agents (like omega-3 fatty acids) could be used to counteract oxidative stress and inflammation caused by prolonged space travel, antioxidants (such as Vitamin E and C) and anti-inflammatory agents (like omega-3 fatty acids). While not strictly pharmacological, the use of exercise mimetics or drugs that mimic the effects of physical activity, such as AMP-activated protein kinase activators can help maintaining cardiovascular health (Kim et al., 2016).

2.4.2. Emerging therapeutic approaches

While early vascular aging is known to be a major cardiovascular threat for long-term spaceflight (Hughson, 2016, Boutouyrie et al., 2022), novel drug administration routes and delivery methods that allow for less frequent dosing, such as monoclonal antibodies (mAbs), small interfering RNA (siRNA) or nanobodies in the future, should therefore be key components of future investigations. These approaches can optimize dosing schedules, reducing the need for frequent drug intake, thereby improving compliance and convenience for astronauts on long-duration missions. In this respect, proprotein convertase subtilisin/kexin type 9 (PCSK9) is a promising therapeutic target as has a

well-known involvement in cholesterol metabolism, but also in the regulation of cardiometabolic aging (Csiszar et al., 2024, Matyas et al., 2023). The development of PCSK9 inhibitors, such as alirocumab and evolocumab, humanized monoclonal antibodies for treating dyslipidemia, (Zhang et al., 2018, Kasichayanula et al., 2018) has been compellingly demonstrated in an extensive array of clinical trials (Rifai and Ballantyne, 2021). PCSK9 inhibitors are administered subcutaneously every 2 weeks or once a month, depending on the indication. A recent milestone in PCSK9-targeted therapy involves the inhibition of liver PCSK9 synthesis using a siRNA molecule inclisiran (Ray et al., 2017). The recommended dosage of inclisiran, is 284 mg administered as a single subcutaneous injection initially, again at 3 months, and then every 6 months.

Others siRNA drugs have been developed for the treatment of dyslipidemia (olpasiran) (O'Donoghue et al., 2022) by reducing lipoprotein (a) synthesis in the liver and hypertension (zilebesiran) (Desai et al., 2023 Jul 20, Bakris et al., 2024) by inhibiting hepatic angiotensinogen synthesis, and has gained significant attention as potentially revolutionizing the prevention of cardiovascular diseases and lipid management.

Additional factors, such as chronic low-grade inflammation and immune-mediated mechanisms, are known to contribute to tissue damage and impaired cardiac and arterial structure/function (Zanoli et al., 2020). Therefore, reducing vascular inflammation could positively impact vascular remodeling in various cardiovascular diseases. One approach is to use pharmacological countermeasures that target key immune pathways, such as IL1 and IL6, known for their cardioprotective effects, or immune checkpoints and tyrosine kinase inhibitors, known for their cardiotoxic effects (see (Zanoli et al., 2020) for review), and at the same time, maintain the balance between stimulating and suppressing the immune system.

Another strategy is to target the resolution of inflammation, a crucial process for restoring tissue homeostasis. Specialized pro-resolving mediators like resolvins, maresins, and lipoxins limit immune cell infiltration and initiate tissue repair. Evidence suggests that inadequate resolution may underlie common vascular diseases such as atherosclerosis and aortic aneurysm. Clinical trials using specialized pro-resolving mediators precursors (EPA: eicosapentaenoic) in the JELIS (Yokoyama et al., 2007) and REDUCE-IT (Bhatt et al., 2019) trials, have shown reduced cardiovascular risk in patients with high triglyceride levels and cardiovascular risk. These findings suggest that specialized pro-resolving mediators could offer a new therapeutic strategy for treating cardiovascular diseases linked to vascular remodeling (Campo del et al., 2022).

Recent developments with protein glycation inhibitors and radioprotective countermeasures for the prevention of early vascular aging yielded promising results (Mayo et al., 2000, Toprak and Yigitaslan, 2019, Wu et al., 2011, Wang et al., 2019, Wang et al., 2019). To date, a number of drug classes have shown encouraging results in limiting radiation-induced cardiovascular and kidney damage (Boutouyrie et al., 2021, Patel, 2020, Cortese et al., 2018, McLaughlin et al., 2017, Langell et al., 2008, Meerman et al., 2021), but none have yet been investigated in the space environment.

Prior to any use in space, all strategies should be approved for use in humans, ensuring optimal drug choice and dosing regimens, for safe effective treatment. Only then pharmacological countermeasures can be tailored to the potential needs of each crewmember during spaceflight. These countermeasures, combined with regular monitoring and adjustments, can help mitigate the adverse effects of microgravity on the cardiovascular system.

Further challenges will have to be overcome if pharmacological countermeasures are to perform as intended. These include muscle wasting, and more broadly, any changes in body composition such as glucose intolerance, fat redistribution and bone depletion, which interfere with PK/PD of pharmacological countermeasures.

2.5. Challenges for space pharmacology

2.5.1. PK/PD alteration in space: what is expected?

Evaluating therapeutics in space presents several challenges, similar to those in rare disease treatment, including a limited number of astronauts (just over 600 astronauts to date and only 24 astronauts beyond LEO, with an average of 7 astronauts in orbit onboard ISS), making it difficult to recruit sufficient participants for classical clinical trials. Moreover, the heterogeneity in drug response among astronauts, without validated biomarkers, complicates the standardization of therapeutic protocols.

Because of the small number of astronauts, the paucity of pharmacological data, either PK or PD, and the rarity of hard endpoints, at least during missions makes it unlikely that pharmacological countermeasures will reach gold standard level of proof for being proposed to astronauts. This poses difficult ethical and reglementary questions that have not been addressed yet. Pharmacological treatments prescribed in astronauts are symptom-driven, and largely rely on past experience, not on clinical evidence. Preventive treatments for space-induced body alterations pose different problems. Evidence (safety/efficacy) will have to come from related conditions in terrestrial diseases, and proof of efficacy from the careful monitoring of substitution criteria along and after the missions.

Few pharmacological countermeasures have been tested during Earth-based simulation of the physiological changes caused by microgravity (head-down tilt bed rest), and none rigorously studied during spaceflight. Currently, drugs are administered under the assumption that they act identically as on Earth. Doses for the few medications that are used on a regular basis in the ISS (antiemetics, analgesics, sleep and vigilance aids, antihistamines) (Wotring, 2015), rely on Earth-based experiences. Our priority recommendation should rapidly be given to robust studies of pharmacological countermeasures in spaceflight, to document empirically-based knowledge and patient/astronaut experiences, clarifying PK/PD in spaceflight.

Space-induced changes in spaceflight may likely impact PK, affecting each step, including drug absorption, distribution, metabolism, and excretion (Gandia et al., 2003, Gandia et al., 2006, Saivin et al., 1995, Kates et al., 1980, Schuck et al., 2005, Levy, 1967), with varying effects for each drug. Whether spaceflight-associated PK alterations actually do modify the therapeutic effect of drugs has yet to be determined, but crucial for both preventive and acute treatments, to avoid medication-related issues far from Earth.

In preparing astronauts for long-duration spaceflight, preventive pharmacological treatments are essential to mitigate potential health risks, including cardiovascular issues, however the benefit/ risk balance needs to be leveraged. Administering preventive medication to healthy individuals may lead to unforeseen adverse reactions, which may be exacerbated by the unique conditions of space. Ensuring that preventive measures do not compromise overall well-being is critical for the success and the safety of extended missions.

Data on how spaceflight affects PD or PK of pharmaceuticals is sparse, primarily based on Earth observations. High dosages are often required to achieve the full benefit on markers of cardiovascular risk factors, such as holds for antihypertensive drugs, (Laurent, 2021) and whether such high dosages are necessary to obtain similar protective effects in space is unknown. Additionally, there are concerns about the risk of dose-related adverse effects when increasing medication dose, especially with prolonged use or as prophylaxis for predicted cardiovascular conditions. Currently, the spaceflight data are insufficient to predict which individuals are at risk of cardiovascular conditions, or whether high-dose pharmaceuticals should be given to all astronauts. The wide-ranging expertise of astronauts may make them less sensitive to certain intangible side effects such as myalgia, that are largely dependent on the nocebo effect (Howard et al., 2021).

Approximately 80% of all drugs are primarily metabolized by CYP (cytochrome P450) isoforms, notably CYP1A2, 2D6, 3A4, 2C9, and

2C19, and spaceflight inflammation is likely to affect their enzymatic activity (Eyal, 2020). In that case, they may alter treatment response by increasing intra- and interindividual variability in terms of drug exposure. This has particular clinical relevance for drugs with a narrow therapeutic range. Indeed, inflammation down-regulates drug-metabolizing enzyme and transporter expression and function at transcriptional and protein levels by a transcriptional and translational inhibitory mechanism (Stanke-Labesque et al., 2020). One example is the increased exposure to verapamil in patients with rheumatoid arthritis (Mayo et al., 2000). As in the general population, slow-metabolizers phenotype astronauts might be selected, so it is essential to adjust dosages, as individual variability can be exacerbated during spaceflight. Maintaining therapeutic margins and concentration consistency is essential to avoid adverse effects. It is essential to determine if the concentration-effect relationships observed on Earth are maintained in spaceflight and if dosages are accurately respected.

Sex also has implications on the PK/PD properties of widely used drugs (Vinge, 1998, Islam et al., 2017), with women often underrepresented in clinical trials (Goldstein and Walensky, 2019), and spaceflight studies are no exception (Corlett et al., 2020). Differences in drug metabolism and a failure to adapt drug dosages to body mass may partly account for the greater incidence of adverse effects in women. In addition, hormonal changes during the menstrual cycle, with contraceptive use and with age also play a role in sex-specific PK and drug exposure (Kashuba and Nafziger, 1998, Beierle et al., 1999, Meibohm et al., 2002), in addition to interindividual variability. In terms of PD, women appear to be more prone to torsades de pointes with drugs such as quinidine and procainamide (Fletcher et al., 1994). Most female astronauts use oral contraceptives during spaceflight (Jain and Wotring, 2016), posing additional risks like hypertension, fluid retention and thrombosis, hormonal changes and drug interactions could be exacerbated during spaceflight.

Interethnic differences in drug response, while not studied in spaceflight, could also impact efficacy and safety. By example, angioedema following treatment with angiotensin converting enzyme inhibitors is three to four times more frequent in Black individuals than in those from other racial and ethnic groups (Kostis et al., 2004).

These sex-specific and interethnic physiological differences could have notable implications for therapeutic efficacy and safety of drugs during spaceflight (Dello Russo et al., 2022). Greater inclusion of sex and ethnicity categories in future PK/PD studies in the space environment would provide valuable data to fill the current knowledge gap.

Empirical studies are needed to improve our understanding of space-induced changes affecting pharmacological countermeasures in space environment, to determine the most effective dosages for optimal efficacy with minimal adverse effects. This will enhance the safety and efficacy of pharmaceuticals in the space environment.

2.5.2. Drug stability and dosage

The administered dose influences pharmacokinetic parameters such as the area under the curve (AUC) therefore biological responses and therapeutic or toxic effects. Space is an ideal reactor for generating molecules essential to life (panspermia) (Panspermia - an overview), so chemical modifications of organic molecules that constitute drugs are thus likely to be expected by exposition to space conditions. On Earth, the magnetic field, the atmosphere and the packaging of drugs limit high energy radiation exposure and resultant degradation and neo-synthesis of chemical compounds. The unique environmental and physical factors encountered in space including excessive exposure to radiation, microgravity, vibration, and varying humidity and temperatures are known to affect the human body but are also factors altering the stability of pharmaceutical preparations (Thirsk et al., 2009). Pharmaceutical instability in space can be caused by changes in the physicochemical properties, which in turn may lead to inefficacy or unexpected toxicity (Davido et al., 2024), and thus to therapeutic failure. While preserving astronauts' health must be a priority for future space missions, national space agencies currently lack consistent and comprehensive data about the stability of pharmaceutical preparations on the ISS. The efficacy of certain medications is known to extend beyond the expiration date (Davido et al., 2024) and yet there is still insufficient evidence to characterize stability beyond LEO for long-duration spaceflight.

Although data are scarce, there is also evidence of a more rapid degradation of medications onboard the ISS than on Earth (Du et al., 2011). A number of drugs used to treat cardiovascular indications—including furosemide, atorvastatin, lidocaine and metoprolol—were reported to have faster degradation or a lower active pharmaceutical ingredient content during spaceflight (Du et al., 2011) . Drugs with other indications such as aciclovir, ciprofloxacin and clotrimazole, which were reported to have faster degradation and lower active pharmaceutical ingredient than the respective ground controls (Du et al., 2011). Thus, after 28 months in space, a notable number of drugs failed to reach the United States Pharmacopeia active pharmaceutical ingredient requirements. The number of drugs concerned increased with the amount of time spent in space, irrespective of the expiry date (Du et al., 2011). Despite providing evidence of drug instability in space conditions, these studies suffered from small sample numbers or a lack of appropriate controls (Eyal and Derendorf, 2019). All space drug stability studies have focused on medications repackaged into non-protective containers, which may lead to potency loss. Evaluating current repackaging effects and developing protective strategies are crucial to ensure medication stability during space missions (Reichard et al., 2023). Although very few changes in drug composition have been reported in space, the risk of consequences on therapeutic properties remains. This was recently illustrated on Earth by changes in the formulation of l-thyroxin, which fulfilled the generic drug regulation requirements but nevertheless caused a massive wave of side effects, most of which were related to non-equivalence in activity (either hyper or hypo), and which should have fallen in the grey zone of bio-equivalence (Concordet et al., 2019, Casassus, 2018). This is analogous to observations with generic drugs (Lechat, 2022), where supposedly equivalent dosage forms can have notable interindividual variability, which possibly explains the different efficacy/tolerability levels between patients.

2.5.3. 3D printing for personalized drugs

The distance from Earth to Mars highlights the logistic problems for drug supplies. In the case of the jugular thrombosis reported in an astronaut, resupply was possible but delayed, and this delay left no other option than temporary use of a suboptimal dosage (Auñón-Chancellor et al., 2020). Resupply for long space missions is not possible since the travel time for both astronauts and the resupply ship are the same, and more importantly, exceed the recognized safe, effective shelf-life of most drugs. The unavoidable consequence is that pharmaceutical preparations will need to be manufactured during space missions (Sawyers et al., 2022). Extended distances from Earth also put severe restrictions on interactive telemedicine that played a significant role in the accurate diagnosis and treatment of the thrombosis case mentioned above. *In situ* production of medicines could be rendered possible via innovative methods such as combining synthesis of cell-based or cell-free therapies with 3-D printing/additive manufacturing (Williams et al., 2022). Several 3D bioprinting experiments have been conducted on the ISS, where minimal gravity eliminates the need for scaffolding to support complex tissue shapes. Redwire Corporation developed the biofabrication Facility as part of the U.S. National Lab's goal to use microgravity for bioprinting human organs. So far, the biofabrication facility has been used to bioprint meniscal and cardiac tissue, although scientific publications on these studies are still lacking (Van Ombergen et al., 2023). Recently, the feasibility of processing pharmaceuticals in microgravity was demonstrated with ritonavir (an HIV protease inhibitor) (Bauser et al., 2024) in on-orbit crystallization experiments, which were recovered and analyzed after reentry to Earth. However, the unique conditions of space pose significant challenges to successfully

implementing 3D (bio)printing for personalized medicine, making it necessary to develop targeted research in this area (Katakam et al., 2024, Tabury et al., 2023).

Additionally, 3D printing in personalized drug delivery has gained interest, particularly for addressing the metabolic syndrome. This technology enables the creation of formulations that deliver precise doses tailored to patient needs and customized drug release profiles, meeting individual therapeutic and nutritional requirements (Alqahtani et al., 2023). 3D printing was utilized to produce low-dose antihypertensive polypills containing atenolol, ramipril, pravastatin, aspirin, and hydrochlorothiazide (Khaled et al., 2015), and four antihypertensive drugs irbesartan, atenolol, hydrochlorothiazide and amlodipine (Xu et al., 2020). Although successful in its fabrication, an unexpected chemical reaction between the polymer and drugs was observed. Issues related to 3D-printed medications of different therapeutic classes that could be relevant to long space missions are detailed in Bácskay et al paper (Bácskay et al., 2022).

2.5.4. *Prolonged pharmacological action to reduce storage and resupply*

Alternately, innovative approaches such as siRNA, monoclonal antibodies therapeutics, or other specific long-acting regimens, could be used to treat certain medical conditions via a single injection every few months, thus resolving the refill issue. For instance, inclisiran, a siRNA blocking PCSK9 enzyme gene translation has hypocholesterolemic action up to 6 months (Ray et al., 2017). Similarly, zilebesiran, siRNA blocking the expression of the angiotensinogen gene lowers blood pressure for more than 6 months, and an antidote is available in case of emergency (Desai et al., 2023). The prolonged pharmacological action (several months) of these molecules means treatment can be administered early in the space mission, reducing the need for storage and resupply, while improving astronaut adherence.

2.5.5. *Logistical and technical constraints of biological sampling*

The very few PK experiments that have been conducted during spaceflight to date have suffered from significant limitations, namely logistical and technical constraints. To date, the PK of only four drugs have been studied on board the American space shuttle and onboard space stations (MIR and ISS), namely acetaminophen (a non-salicylic analgesic and antipyretic) (Cintron et al., 1987, Putcha and Cintrón, 1991, Kovachevich et al., 2009, Polyakov et al., 2020), scopolamine/-dextroamphetamine (an antiemetic-anticholinergic/stimulant) (Cintron et al., 1987, Putcha and Cintrón, 1991), promethazine (an antiemetic-histamine H1 receptor antagonist) (Boyd et al., 2009), and antipyrine (used as a marker of hepatic clearance) (Kovachevich and Putcha). Although changes in PK were observed, methodological limitations prevented firm conclusions. However, various factors known to affect PK, like interindividual differences, small sample size, non-standard collection technique such as saliva sampling, and sample collection time, are reminders that observations such as these must be considered with caution. We recommend the development of a methodological framework to simplify PK studies of common drugs under both actual space flight and microgravity simulation conditions. Overcoming logistical issues and making fundamental changes to traditional practices is essential for meaningful PK studies during spaceflight.

In this respect, blood sample collection at regular intervals is complicated, and despite the risks of injury and exposure to blood-borne pathogens, plasma sampling is routinely performed. However, multiple sampling over time interferes with other duties and further complicates the task. Consequently, saliva sampling only has been used so far for PK/PD studies during spaceflight, even though it has not yet been validated against Earth conditions (Kamali et al., 1987, Sanaka et al., 2000, Smith et al., 1991). Major differences between saliva sampling results for acetaminophen in spaceflight and in simulated weightlessness (head--down bed rest) studies hinders direct comparisons (Gandia, 2003; Kamali et al., 1987). Saliva sampling offers non-invasiveness and ease of collection, but has significant limitations, as salivary concentrations do not always accurately reflect blood concentrations, limiting its utility for biomonitoring many drugs, some drugs affecting saliva production, like scopolamine (Smith et al., 1991). The lack of standardized collection and processing methods affects the reproducibility and comparability, and there is no reliable way to correct for individual hydration differences. Saliva composition varies greatly due to factors such as age, sex, diet, and oral health, and may change during flights (Hand et al., 2020).

Plasma remains the gold standard for pharmacology analysis because it directly reflects circulating drug exposure (Dash et al., 2021). Urine is also interesting for microsampling as it reflects drugs primarily eliminated by the kidneys and is non-invasive. Additionally, the absence of proteins and cellular material in urine makes pretreatment less fastidious than for plasma samples. The choice of matrix depends on the drugs (or metabolites) to be detected, including the prescribed dose, plasma half-life, conversion of a prodrug into its active metabolite, and the fraction excreted unchanged in urine. Blood plasma measurements may be more specific, especially for drugs with low bioavailability or limited renal excretion, such as candesartan. The non-detection of lercanidipine in urine can be explained by its extensive first-pass metabolism by CYP3A4.

Furthermore, multiple samples need to be fast-frozen and stored for their return to Earth for analysis, which adds to the complexity. Other strategies for collecting biological fluids need to be developed to reduce the logistical and technical constraints and make in-flight PK studies possible (Derobertmasure et al., 2024, Derobertmasure et al., 2023, 2025). Liquid chromatography with tandem mass spectrometry has significantly reduced sample volumes required to assess drug concentrations in biological fluids. Microsampling methods that require 50 µL or less of biological fluids are being more widely used in pre-clinical and clinical PK studies (Spooner, 2019, Guerra Valero, 2021) and in therapeutic drug monitoring (Tey and See, 2021, Morgan, 2021), and are rapidly emerging as an alternative to classic biological sampling methods to assess drug concentrations of active pharmaceutical ingredients in response to the different constraints encountered in space. In this light, the feasibility of dried urine spot (DUS) and dried blood spot (DBS) sampling in microgravity was demonstrated during a parabolic flight campaign and mars analogue missions, aimed at detecting potential cardiovascular drug candidates to prevent early vascular aging in astronauts (Derobertmasure et al., 2024, Derobertmasure et al., 2025). DBS sampling is already used on Earth for monitoring adherence to several cardiovascular drugs (Peeters et al., 2020, Peeters et al., 2022, Peeters et al., 2024, Smith et al., 2012, Peeters et al., 2020) and has been validated during parabolic flight through a caffeine PK study campaign as a proof of concept (NCT06431984) (Derobertmasure et al., 2024). The DBS method was also used during the Inspiration4 mission for collecting biospecimens for the space omics and medical atlas (Overbey et al., 2024).

Ideally, in-mission analysis facilities as point-of-care-testing should not require samples to be frozen and returned to Earth (Wiencek et al., 2023). Innovations in space laboratory medicine could facilitate the development of PK studies in space.

The efficacy of medications is closely linked to the exposure levels, which are monitored through various biological markers that will be explored in the following section. This raises essential questions: Does the therapeutic range of a specific drug remain consistent in space? How can we measure and predict it accurately?

3. Biological biomarkers in space pharmacology

The BEST glossary of the FDA defines seven biomarker categories: susceptibility/risk, diagnostic, monitoring, prognostic, predictive, pharmacodynamic/response, and safety (FDA biomarkers politics 2025). Each biomarker must comprise a full description including the biomarker name, the physiological source/matrix, and detailed metrological data. A biomarker may also consist in a panel of multiple characteristics, like omics or deep phenotyping. Qualified biomarkers have

the potential to provide valuable information that may reduce uncertainty in regulatory decisions during drug development, which is particularly crucial for space research. Each biomarker undergoes a formal regulatory process, within the stated context of use.

3.1. Pharmacogenetic insights

Pharmacogenetics provides crucial insights into the interindividual variability in PK, particularly regarding drug metabolism via CYP450 enzymes. These enzymes are fundamental to personalized medicine, influencing dose adjustments, contraindications, and the selection of drugs to prevent adverse effects and optimize therapeutic efficacy.

Genotyping can predict CYP450 activity by identifying specific alleles, providing an immutable genotype for each patient. The potential of pharmacogenomics testing during astronaut training lies in anticipating and understanding the extent and type of drug-drug interactions, thereby optimizing personalized drug prescription in space (Stingl et al., 2015).

In this respect, CYP2D6 is involved in the metabolism of 11 drugs on the ISS, (Wotring, 2015) including the beta-blocker metoprolol (Stingl et al., 2015). Significant genetic polymorphism in CYP2D6 means poor metabolizers may experience adverse effects like bradycardia, while rapid metabolizers may face therapeutic inefficacy. Similarly, CYP2C9 metabolizes many important drugs, including phenytoin, anti-epileptic drug (in the ISS medical kit and which has a narrow therapeutic index) and the angiotensin II type 1 (AT1) receptor antagonists, losartan and irbesartan (Sangkuhl et al., 2021). These AT1 receptor antagonists could be used to prevent space-induced early vascular aging. Genetic polymorphism in CYP2C9 influences the clinical response to treatments with these antagonists (Cho et al., 2023). Additionally, a polymorphism in the solute carrier organic anion transporter family member 1B1 gene encoding the drug transporter organic anion transporting polypeptide 1 (OATP1B1) is associated with an increased risk of myopathy during statin therapy (Carr et al., 2019, Research C for DE and 2022).

Ideally, pharmacogenomic models should consider sources of variability at multiple levels including genetics, epigenetics, and potential drug interactions (induction, inhibition) (Gertz et al., 2020). In the absence of any data on physiological changes occur during spaceflight, Earth-based PK/PD is a proxy for predicting and optimizing drug therapies in space. Technologies, such as proteomics and DNA sequencing, provide inter-individual variability for disease identification and personalized treatment. This was exemplified by the astronaut Twins Study (Garrett-Bakelman et al., 2019), which focused on molecular biology measurements to compare the effects of spaceflight on two twins, one on a 340-day mission, while the other was observed during this period on Earth. Multiple changes were observed giving a glimpse of how long-duration spaceflight affects an individual astronaut's physiology.

3.2. Therapeutic drug monitoring

While genotyping identifies genetic variants, it does not always predict their functionality. Thus, phenotyping, which measures CYP enzyme activities, is a complementary approach. This involves administering orally specific xenobiotics metabolized by CYP enzymes, followed by blood or urine sampling. Since most pharmacological countermeasures are eliminated mostly by hepatic metabolism, and their clearance can be delayed by inflammation, making blood drug concentration monitoring acceptable for such case.

Integrating therapeutic drug monitoring (TDM) could be an ideal strategy to assess PK variability and ensure drug exposure management. TDM involves measuring medication concentrations in plasma or whole blood generally to optimize therapeutic efficacy while minimizing side effects, and is particularly useful when a pathological condition affects drug PK. Despite its proven benefits in personalized medicine, TDM has not yet been implemented during spaceflight. Thus, lidocaine, a class IB antiarrhythmic used for ventricular tachycardia, including in the ISS space medical kit, requires TDM due to its variable plasma concentration and direct concentration-effect relationship, with CYP3A4 mainly responsible for its metabolism (Campbell and Williams, 1998).

Monitoring cardiovascular drug concentrations in astronauts' blood will be beneficial in several spaceflight scenarios including adjusting doses when treatments are ineffective, managing adverse drug reactions, confirming and managing PK drug interactions, assessing treatment efficacy when conditions change, introducing new pharmaceutical forms, and identifying poor medication adherence. Blood drug concentration monitoring of preventive cardiovascular pharmacological countermeasures against early vascular aging or thrombosis will be crucial for ensuring the safety of pharmacological countermeasures therapy. Monitoring drug concentrations directly in the blood is the only method that can integrate all the unique spaceflight conditions. For antihypertensive drugs, efficacy is generally measured by monitoring blood pressure rather than drug concentrations in blood, as there is no clear relationship between dose and blood drug concentrations. TDM of antihypertensive drugs is mainly used to identify non-adherence but can also improve therapy for specific populations. In the general population, many cardiovascular medications are taken prophylactically and do not usually produce an immediately noticeable effect, leading patients to undervalue their importance. It is likely that astronauts might similarly undervalue such medications used to prevent space-induced early vascular aging.

While sex differences in dosage and side effects are recognized, limited studies have used TDM to investigate these variations. One study on metoprolol showed that females had higher peak concentrations and a higher average area under the curve compared to males (Versmissen et al., 2024), highlighting the need for more research in this area.

The integration of TDM could be useful for guiding the use of novel long-acting treatments aimed at preventing cardiovascular events in astronauts, such as monoclonal antibodies and siRNA therapeutics. These advanced therapies offer promising benefits but come with unique PK and PD challenges that necessitate careful monitoring. The PK variability of monoclonal antibodies and siRNAs, usually quite broad, needs to be precisely described as it influences the variability of their clinical effect. They both have a distinct PK profile compared to traditional drugs. Typically administered parenterally, they exhibit a long terminal half-life and high pharmacological specificity. The bioavailability of monoclonal antibodies, such as PCSK9 inhibitors, ranges from 40% to 70% and may cause injection site reactions. The elimination of monoclonal antibodies occurs primarily through pinocytosis and proteolytic degradation or via immune complex elimination (Kasichayanula et al., 2018, Paintaud, 2009, Ternant and Chhun, 2019). Their PK can be highly variable and often nonlinear, influenced by factors such as immunization, body size, albumin concentration, antigen mass, and inflammation. Studies on anti-PCSK9 monoclonal antibodies have shown that statins can increase their clearance, possibly by enhancing PCSK9 secretion and the formation of monoclonal antibody-PCSK9 complexes, leading to accelerated antibody elimination (Ternant and Chhun, 2019). siRNA therapeutics unlike conventional drugs, are not metabolized by traditional drug-metabolizing enzymes or transporters, making drug-drug interactions rare (Jo et al., 2023). However, the unique PK characteristics require specific attention in TDM. Additionally, the risk of persistent side effects from long-acting drugs after administration must be considered.

Optimizing the routes of drug administration is crucial for in-flight medication efficacy, and TDM plays a vital role in this process. Most in-flight medications are administered orally, followed by intranasal, intramuscular, and rectal routes in decreasing order of frequency (Putcha et al., 1999). Studies on space-motion sickness conducted in conditions of weightlessness suggest that intramuscular administration is an effective alternative to the oral route (Gandia et al., 2006, Boyd et al., 2009). Space adaptation syndrome, characterized by vomiting, diarrhea and dizziness, affects approximately 70% of astronauts (Weerts

et al., 2015; Martina and Paloski, 2006) and is an example of the challenges of suboptimal absorption with oral drug administration if vomiting occurs.

To increase the applicability of TDM, multiple studies report the development of a dried (DBS) test or volumetric absorptive microsampling using whole blood obtained by a fingerprick (Versmissen et al., 2024). The main advantage of this method is its ease of use. Indeed, the blood spot can be obtained anywhere anytime by either a healthcare provider or even the patient themselves.

Key gaps:

- How to conduct TDM appropriately onboard ISS (e.g., choice of the drugs, the biological matrix, the sampling method and the appropriate timing of biological fluid sampling).
- Ideally develop non-invasive sensors for drug dosages
- How to interpret blood (or other fluids) drug concentrations?

3.3. Pharmacodynamic (PD) biomarkers

3.3.1. Identification and significance of PD biomarkers

The effects of preventive cardiovascular pharmacological countermeasures cannot be predicted solely by their blood concentrations. Dosage regimens should be determined based on the astronaut's signs and symptoms and PD biomarkers such as blood pressure and electrocardiogram findings. The goal should not be merely to achieve a therapeutic range but to ensure effective and safe drug response. Validating a surrogate endpoint requires evidence that changes in the surrogate reliably predict clinically significant outcomes.

3.3.2. Impact of spaceflight on cardiovascular pharmacodynamics

Clinical research into sarcopenia on Earth has linked the loss of muscle mass to a proportional reduction in vascular density. It therefore follows that the muscle atrophy observed during spaceflight reduces the density of targets of cardiovascular medications (Stehouwer, 2018, Horton and Barrett, 2021, Paolino et al., 2020, Sörensen, 2016). Consequently, the physiological changes within the cardiovascular system during spaceflight are likely to affect the PD properties of medications, and antihypertensive drugs (Graebe et al., 2004), diuretics (Graebe et al., 2004), and ion channel modulators in particular (Goldermann and Hanke, 2001). Microvascular changes are the driving force behind metabolic and muscular changes, (Climie et al., 2019) and are known to trigger a positive feedback loop. The behavior of G-protein-coupled receptors, responsible for cellular communication and targets of numerous medications. Both are likely to be affected by long-term exposure to microgravity through changes in membrane dynamics (Kast et al., 2017, Kohn and Hauslage, 2019) with a knock-on effect on PD within the cardiovascular system. Potential consequences include the need for dose adjustments, changes to classic first-line treatment options, and ultimately for drug selection to be optimized through pharmacogenomics, phenotyping and/or modelling. Further investigations in the space environment are needed to determine whether the PD response to cardiovascular drugs is the same as on Earth. This would require simple accurate assessment of PD, using techniques that are rapid, non-invasive, and provide a direct evaluation of cardiovascular remodeling.

3.3.3. Wearable devices for continuous monitoring

Traditional non-invasive metrics can also be collected using wearables and point-of-care devices (Strangman et al., 2019), including ultrasound, (Law and PaulB, 2011, Scott et al., 2021) blood pressure monitors, smart shirt (Bio-Monitor, 2014) and watches (Medical-Grade Smartwatch Can Monitor Astronauts). These platforms should be minimally intrusive, provide easily interpretable data, and not consume excessive crew time (Scott et al., 2023). In this regard, arterial stiffness, detectable by measuring pulse wave velocity, is an important biomarker for cardiovascular health. Higher pulse wave velocity indicates stiffer arteries, which can lead to increased systolic blood pressure and hypertension, while lower pulse wave velocity suggests better cardiovascular health. Devices like the pOpmètre® is a non-invasive, ergonomic, compact medical device that measures pulse wave velocity by photo-plethysmography (Alivon et al., 2015, Obeid et al., 2017). Its use was validated during an analogue Mars mission at the Mars Desert Research Station (Derobertmasure et al., 2025; COSMOS, 2024). Other recent advancements, such as artificial intelligence (AI) -guided ultrasound augmented reality diagnostics (EchoFinder (Derache and Thevenon, 2022)), enhance non-intrusive monitoring capabilities.

3.3.4. Biological biomarkers for comprehensive assessment

A systematic assessment of inflammation and aging biomarkers (Chen et al., 2023) affecting drug PK/PD is needed. A recent review lists the known potential cardiovascular ageing biomarkers relevant to space along with our current understanding of the underlying mechanisms of cardiovascular ageing (Rehnberg et al., 2023). Recent advances in biosensor technologies for point-of-care urinalysis could benefit and provide continuous and sustainable health monitoring (Hwang et al., 2022).

Combining physiological and molecular biomarker monitoring with an AI-assisted knowledge base can help predict adverse health outcomes and identify preventive actions, crucial for long-term missions (Scott et al., 2023). The VITAL horizon 2020 project aims to propose such approach for the general public, but also highly adaptable for astronaut care (Virtual Twins as tools for personalized clinical care).

3.4. Personalized medicine in spatial environment

Personalized medicine is a diagnostic, preventive, and therapeutic approach of medicine which provides tailored therapy to individual patients based on inter-individual differences and their response, either therapeutic, adverse, or allergic (Mathur and Sutton, 2017, Goetz and Schork, 2018). Pharmaceutical interventions that are tailored to an individual's features (genome, epigenetic, anthropometric etc) are one approach to developing pharmacological countermeasures with the potential to optimize efficacy and at the same time reduce the risk of side effects.

3.4.1. The role of biobanks in personalized medicine for astronauts

Numerous biobanks have been established worldwide to support medical research, including personalized medicine. Biobanks are essential resources for personalized medicine, because they provide references in genomics, proteomics, metabolomics, translational studies, therapeutic target, and identification of new biomarkers and drug discovery. Biobanks contribute significantly to several key aspects of personalized medicine (Kinkorová, 2016):

- Personalization: The development of individualized digital genetic/epigenetic profiles.
- Predictiveness: The ability to predict disease risk based on an individual's genome, combined with factors like age, sex, and environmental data.
- Prevention: The potential to avoid or minimize disease risk factors based on personalized data.

Multiple samples from the same patient collected at different time points in specified clinical contexts are strategic for biomarker investigation, and discovery using multidimensional high-throughput technologies (Annaratone et al., 2021). Applied to space research, this paradigm led to the creation of the Space Omics and Medical Atlas, an international astronaut biobank (Overbey et al., 2024, SOMA, 2024). Space omics and medical atlas is a collection of data and samples from various space missions aimed at standardizing biological sample collection, processing, analysis, and data sharing for clinical, cellular, and genetic research. This biobank facilitates the validation and

comparison of findings among investigators, space agencies and companies worldwide. Longitudinal sampling allows monitoring the impacts of spaceflight and provides health services to the crew post-mission, representing a significant scientific breakthrough for aerospace medicine. Space omics and medical atlas was established using methods from the NASA Twins Study in 2019 (Garrett-Bakelman et al., 2019), which conducted a comprehensive, integrative multiomics analysis of astronauts, including crew from the Inspiration4, Polaris Dawn, and Axiom missions. This biobank has already helped revealing that space missions cause significant changes in gene expression, suggesting astronauts might develop a frailty-like condition (Camera et al., 2024). Epigenetic changes in certain frailty-related genes could serve as bioindicators of space-induced changes, helping to mitigate long-term adverse health effects. Thus, the gene coding for AKT1, linked to growth signals, cell survival, aging, and age-related diseases like cardiac issues and dementia, remained upregulated after re-entry. Inflammation-associated transcriptomic signatures were reported by the Twins Study consistent with mild increases in inflammatory cytokine levels from other studies on astronaut plasma (Zheng et al., 2023). While the multiomic data from the 14 crew represent the largest release of astronaut data to date, the cohort is still small. This represents only a first step towards addressing the many hazards and needs for long-term missions, building towards sufficient statistical power and contextualizing normal human biological variation (Overbey et al., 2024).

To comprehensively evaluate the cumulative impact of microgravity and deep space radiation on the cardiovascular system, we strongly recommend the creation of a cardiovascular biobank. This biobank would collect and compare data from astronauts remaining in LEO with those assigned to lunar missions. The biobank would include biological biomarkers and continuous cardiovascular measurements from both cohorts.

3.5. Space pharmacovigilance

Effective space pharmacovigilance relies on a thorough registry of adverse effects to grasp risks and devise mitigation strategies. Current studies on drug use during space missions lack statistical robustness due to small sample sizes and inadequate data on dosing, therapeutic effects, attitudes toward medication, adverse events, and drug interactions.

One recent study of self-reported medication use by 24 astronauts via a software application showed that drug ingestion (20.6 ± 8.4 medication entries per individual per flight week) was far greater than previous figures had suggested (<12 per person per entire mission) (Wotring and Smith, 2020). While user-acceptability of such software can be improved, tools like EveryWear and DoseTracker applications (Wotring and Smith, 2020, Marnat, 2022) are essential for managing medication inventory, use and efficacy and adverse effect monitoring. Implementing a standardized in-flight system to evaluate therapeutic responses, monitor medication trends, and oversee adverse reactions would be a key component to be included in spaceflight procedures to ensure safe and effective medication use. This approach would provide essential data for adjusting drug dosages, ensuring optimal pharmaceutical care for astronauts. Collaboration among astronauts and medical personnel (flight physicians, pharmacists) is needed in establishing this framework, benefiting government, private entities in space missions, and the wider research community. Adapting terrestrial pharmacovigilance practices for space missions will enhance medication risk management.

Key steps include:

- Drug usage reporting and evaluation: Astronauts and medical staff report adverse effects using specialized software, supported by a network of space pharmacovigilance information centers similar to terrestrial centers.
- Drug risk analysis and management: Investigations analyze risks associated with space medication use, guiding tailored risk management plans. Include drug surveillance in the NASA Integrated Medical Model (Antonsen et al., 2022) to detect medical conditions and evaluate risks related to drug misuse.
- Drug safety profile assessment: Evaluating medication safety profiles, considering unique spaceflight conditions.
- Corrective measures: Implementing necessary adjustments like dosage modifications, usage restrictions, or medication withdrawal as warranted, with communication to astronauts, flight surgeons, and space agencies.
- Communication and dissemination: Regular updates on medication safety are shared with stakeholders, including astronauts, medical teams, and space agencies.
- Public health policy: Contributing to policies that prevent medication-related issues in space, through collaboration with international space agencies and health organizations.

This structured approach ensures safe medication use in space, adapting time-proofed Earth-based practices to the challenges of space environments.

Future investigations should also focus on how medications and cardiovascular pharmacological countermeasures are used during space flight by including perceived efficacy data (subjective), qualitative data, such as perception of the treatment effect and the astronauts' experience of medication use. These data can help identify shortcomings and unmet needs from a patient perspective, which is commonly addressed in terrestrial healthcare but not in spaceflight. Despite methodological limitations, the variability in perceived drug efficacy highlights the need for further research focused on qualitative data, providing evidence from an astronaut-centered perspective (Sawyers et al., 2022, Wotring and Smith, 2020).

3.6. In vivo human spaceflight analog simulations

The infrequency of spaceflight and the difficulty of conducting experiments in actual microgravity necessitate ground-based simulations to understand adaptation mechanisms and develop and evaluate countermeasures. Ground-based models allow the study of cardiovascular effects of physical inactivity without other vascular risk factors, focusing on macro- and microcirculatory levels. Head-down bed rest (HDBR) (Pavy-Le Traon et al., 2007), and dry immersion provide recognized models for studying the effects of global physical inactivity in healthy individuals (Navasiolava et al., 2011). HDBR, where participants lie with their heads slightly lower than their feet at a -6° angle, is a well-established and widely used terrestrial simulation of the physiological effects of microgravity (Pavy-Le Traon et al., 2007, Hargens and Vico, 2016). This model replicates cardiovascular, bone, and muscle changes observed in weightlessness. HDBR studies often test several countermeasures, each targeting a specific physiological function, akin to the multifaceted approach needed during spaceflight. Nutritional with potential cardiovascular effects have been tested using microgravity analogs with mixed results (Navasiolava et al., 2020), however, pharmacological countermeasures have not been tested. A recent review has highlighted the negative cardiovascular health consequences that typically increase with the duration of bedrest, drawing parallels with the effects observed over decades of aging (Mastrandrea et al., 2024). For instance, a 60-day HDBR study using antioxidant/anti-inflammatory supplements, including resveratrol, polyphenols, vitamin E, selenium, and omega-3, did not prevent vascular changes. There was a significant increase in aortic stiffness, equating to about 11 years of vascular aging, which did not fully recover a month post-HDBR (Boutouyrie et al., 2022).

Despite extensive use of HDBR as a microgravity-effect simulation, no study has compared physiological adaptations of the same astronauts in actual versus simulated microgravity (Norsk, 2020). These simulations are limited by the incomplete removal of gravity stress, and by the absence of cosmic radiation. Although they induce deconditioning close to real weightlessness, the underlying mechanisms differ (Hargens and

Vico, 2016, Watenpaugh, 2016). Currently, both the bed rest and dry immersion model have not been used for PK/PD studies. The results are challenging to interpret due to confounding factors such as daily stress, unaccounted for activities, and complex protocol designs.

4. From bench to bedside

4.1. In vivo experimental approaches: animal models

Techniques like hindlimb unloading by tail suspension in rodents simulate the fluid shifts seen in actual microgravity, providing critical insights into cardiovascular responses and aiding in the development of countermeasures. These models have revealed significant cardiovascular changes, such as altered heart rate, exercise capacity, peripheral arterial vasodilatory responsiveness, and baroreflex impairment. These findings are qualitatively similar to those observed in humans during spaceflight or head-down tilt simulations, making rodent models relevant for space biomedical research (Powers and Bernstein, 2004).

Long-term simulations in mice, using hindlimb unloading, also induces carotid artery changes akin to aging, including stiffening, fibrosis, and increased senescence markers. These effects are mediated by the mechanotransducer Piezo1 and miRNA (miR-582–5p), which promote collagen deposition in vascular smooth muscle cells (Zhang et al., 2024). Such models are essential for studying the mechanisms behind cardiovascular aging in space and testing potential interventions. Furthermore, spaceflight and simulated microgravity by tail suspension have various effects on hepatic biotransformation enzymes in experimental rodents, affecting xenobiotic metabolism and potentially altering therapeutic outcomes (Vinken). Notably, there are species (rats vs. mice) and sex differences, highlighting the need for careful model selection.

The tail-suspended rat model also offers valuable insights into the PK/PD changes associated with weightlessness (Feldman and Brunner, 1994). By studying hepatic and renal physiology under these conditions, researchers can better understand drug metabolism during space missions. The ability to produce transgenic and gene knockout models in rodents, including tissue-specific conditional knockouts, enhances the study of cardiovascular adaptations to microgravity and the development of personalized medicine.

These animal models are crucial for optimizing personalized treatments, guiding clinical trial design for astronauts, and testing countermeasures. While humanized models provide valuable insights despite their limitations (Aartsma-Rus and van Putten, 2019), including differences in metabolism, immune response, and lifespan compared to humans, as well as ethical concerns and high costs. By integrating genome expression, external factors, and computational tools, animal models will advance precision medicine for space missions.

4.2. Spheroids, organoids and organ-on-a-chip technology in personalized medicine for astronauts

The limited number of astronauts in space and the prohibitive cost and challenges of conducting animal studies in space restrict our ability to study the space environment. These limitations make it difficult to develop or repurpose drugs using standard methods that require large numbers of animals or human subjects. Thus, spheroids, organoids and organ-on-a-chip technology are interesting for studying space effects and developing space-specific treatments. They enable dynamic studies of the microenvironment, reduce the use of animal models, and support novel drug development, efficacy, and toxicity assessments (Wang et al., 2024).

Spheroids are aggregates of cells from similar origin, where organoids are small 3D models that mimic the structure and function of organs (Zhao et al., 2022). Generated from an individual's stem or progenitor cells, they are excellent tools for personalized approaches. Spheroids and organoids develop similarly to organs, making them realistic models for studying human tissues without harming individuals. For example, cardiac organoids and vascular beds have been used to study cardiac diseases and drug responses on Earth (Roshanravan et al., 2023). However, spheroids and organoids can develop variably, and controlling their environment is challenging.

Organ-on-a-chip technology involves growing cells from relevant organs within a fabricated device that mimics some of the organ's functions and environment, allowing precise control over the cells and their microenvironment. Organ-on-a-chip systems capture human physiology and pathophysiology from a different perspective than organoids, making them suitable preclinical models for clinical transformation and precision medicine. These microfluidic devices integrate biological systems and allow for mechanical and electrical stimulation when needed (Paloschi et al., 2021).

By combining organoids with organ-on-a-chip platforms, both macro- and microvasculature can be integrated. Considering that the vasculature is a primary target for radiation and microgravity-related aging processes, vascularization is crucial for studying the effects of the space environment (Tabury et al., 2023, Shakeri et al., 2023). These techniques offer a promising approach for modeling vascular diseases and ageing by incorporating multiple cell types, mechanical and biochemical cues, and fluid flow in a microscale platform (Shakeri et al., 2023).

Numerous experiments on the ISS since 2018 have focused on human stem cells and their differentiation into cardiac progenitor cells or cardiomyocytes, and others have been accepted to significantly advancing our understanding of heart tissue engineering in space (Tabury et al., 2023). One notable project, AstroCardia (Welcome to AstroCardia), involves a collaboration of five Belgian companies and research centers to study cardiac aging. They plan to send a miniature artificial heart to the ISS in 2025, using 3D bioprinting to develop a heart-on-a-chip model. This research aims to study the effects of the space environment on the heart and understand how these effects relate to cardiac aging on Earth. These studies will be fully automated and can be conducted remotely. If successful, it could renew our understanding of heart health and lead to new treatments for heart-related issues (Tenreiro et al., 2021).

Organoids can be considered "avatars" of heart and vessel aging, instrumental in answering open questions in translational research and studying cell and tissue responses to specific pharmacological treatments and for personalized spaceflight risk effect prediction. This research represents a step towards personalized medicine, allowing for testing a range of treatments to determine the most suitable option for individual patients. Studying cardiac aging in an accelerated space environment provides research results that are inaccessible on Earth, paving the way for advancements in personalized medicine.

4.3. PK modeling

PK modeling also plays a key role in personalized medicine. *In vivo* PK data in astronauts is limited, but extensive literature is available on the physiological modifications, particularly fluid dynamics in microgravity. Therefore, the bottom-up approach or physiology-based pharmacokinetics, a well-established mechanistic tool, is generally employed to characterize dose-exposure-response relationships (Perry et al., 2020). Physiology-based pharmacokinetics uses physiological and physiochemical data to simulate physiological responses to predict PK profiling. Physiology-based pharmacokinetics modeling offers also the benefit of integrating *in vitro* data to predict drug disposition *in vivo*, particularly when *in vivo* data are not readily available. The physiology-based pharmacokinetics approach could simulate 1) the PK of drugs of interest in our specific astronaut's population, and 2) the PK in different environmental conditions such as microgravity, radiation exposure, and isolation. In microgravity, there is a redistribution of fluid flow in the body, renal, intestinal and hepatic changes, which can affect drug absorption and distribution throughout the body, thereby altering their efficacy. Physiology-based pharmacokinetics models have been developed for cardiovascular drugs, assessing impacts in comorbid

populations such as diabetes and renal disease, which can alter drug disposition and amplify drug interaction risks (Perry et al., 2020, Zamir et al., 2023, Demeester et al., 2023). Additionally, integrating population PK and Bayesian models with physiology-based pharmacokinetics enhances the ability to account for interindividual variability and refine predictions in real time, making these models particularly valuable for this unique space environment.

However, developing these predictive models requires large amounts of data, which are often lacking, especially in space pharmacology. Without comprehensive datasets, there is a risk of producing incomplete models. This is where tools like pharmacovigilance, biobanks, and organoids become essential, providing the data needed to create accurate and reliable PK predictions for space missions.

A recent review (Daniels and Williams) highlights the application of physiology-based pharmacokinetics modeling in optimizing pharmaceutical strategies for exploration spaceflight. Moreover, integrating machine learning and AI with physiology-based pharmacokinetics models promise further enhancements in predicting drug responses and supporting decision-making in space mission planning (Deepika and Kumar, 2023).

4.4. AI-enhanced space pharmacology

AI will affect every step of future space missions. For optimal pharmacological countermeasures, we strongly believe that AI combined with bottom-up modelling will allow to build digital twins (which are computational models of individual patients) for astronauts, integrating space-induced pharmacodynamic and pharmacokinetic changes, based on measured phenotypic changes and genotype.

Space pharmacology can be improved by using AI-modeling systems (Scott et al., 2023, Scott et al., 2021, Sanders et al., 2023) to monitor, gather, and evaluate biomedical data. These systems can analyze and predict individual health risks, adapt to new data, and offer preventive, actionable, and timely insights to deep space crew members and medical staff. Medical digital twins can also predict drug efficacy (Katsoulakis et al., 2024). These digital twins will allow in silico experimentations, and tailoring of treatments for optimal response and safety. This approach aligns with the recommendation workshop organized by the National Aeronautics and Space Administration, on future applications of AI in space biology and health (Scott et al., 2021).

5. Conclusion and recommendation

This paper highlights the current shortcomings and immediate requirements for the development and implementation of pharmacological countermeasures for future space exploration missions, with a specific focus on the cardiovascular system. This example can be followed for any of the physiological systems since all are affected by spaceflight induced body changes. In particular, musculoskeletal, neurological, or immune systems are vital to protect since alterations might affect the completion of the missions (especially BLEO long term missions) or the health of retired astronauts.

Being exhaustive on the potential pharmacological countermeasures would lead us too far outside the scope of the paper. We cannot address all potentially interesting drugs for all physiological systems. For instance, anabolic corticosteroids used rationally could be useful to counteract muscle loss, bisphosphonates to counteract bone loss, and several candidate drugs could be used for limiting the impact of radiations.

The longer durations and longer distances will exert significant impacts on humans therefore on space pharmacology. We call for the development of new pharmacological procedures adapted to spaceflight, as personalized PK profiles based on individual PK and foreseeable space-induced changes. The scarcity of literature calls for systematic studies on TDM and medication stability, to understand dose exposure in space. Additionally, research into processes for manufacturing drugs with extended shelf lives is essential to ensure accurate dosing over long-duration missions.

Space flight cumulates all difficulties, because any logistical and operational parameter has to be accounted for, and because any mistake may lead to catastrophic failure. Limited time for experiments and small numbers of subject add to the challenge for proving the effectiveness and safety of pharmacological countermeasures. This is why this review stresses on the simplicity and robustness of the proposed methods. The aim is to limit the additional burden of pharmacological countermeasures on crews while improving knowledge and providing effective protection. The same applies to logistical constrains, with light, robust methods for monitoring treatments (therapeutic drug monitoring, pharmacodynamic monitoring) being recommended.

Combining pharmacogenomics and pharmaco-phenotyping with TDM will help space medical teams optimize drug management and develop guidelines. The prevalence of genotypes, inflammation state, and their impact on PK, along with TDM's ability to accurately estimate AUC with a limited number of samples, are significant factors. Genotyping/phenotyping in spaceflight can predict drug-drug interactions, while TDM ensures proper dosage and efficacy as PK/PD can change during missions, thus influencing the response to pharmacological countermeasures with varying intra- and interindividual outcomes (Eyal and Derendorf, 2019). Advancements in microsampling and new medical devices and ultimately accurate, non-invasive monitoring, will facilitate TDM and drug effect measurement.

A pharmacovigilance system, adapted to spaceflight is needed to evaluate medication use and side effects. Biobanks like Space omics and medical atlas will help identify new markers for drug monitoring and establish therapeutic targets. Data from organoids, organ-on-a-chip technology, and analog models (human or animal) will enhance personalized PK models, aiming for individualized treatments. Importantly, headway can only be made if sex, gender, and ethnicity hold key positions in these critical considerations.

Personalized medicine is currently restricted to the context of new drugs, particularly those with a narrow therapeutic index for particularly serious health conditions. However, in terms of preventive measures for non-communicable diseases, it is a potentially ground-breaking approach for millions of individuals who will be able to benefit from treatments that are both safe and effective, and necessitate fewer follow-up visits. In terms of cardiovascular diseases, and early vascular aging in particular, billions of people worldwide could benefit from targeted preventive drug strategies. These examples highlight the synergistic link between space travel and global health. Space travel should be viewed as one of several research platforms that enable significant advances to be made in terms of healthcare for humanity as a whole (Scott et al., 2022), an extreme model of what humanity may have to adapt to, one that has and will continue to contribute to the United Nations Sustainable Development Goals, notably 3, 5 and 17 (Committee on the Peaceful Uses of Outer Space and Scientific and Technical Subcommittee 2022).

As recommendations, in many cases the technology and methods already exist to reduce pharmaceutical risk but have not been tested or adopted by the agencies. A paradigm shift is required within the spaceflight organizations (private or public) and the supporting medical community to overcome these obstacles with a new approach to pharmacological studies, targeting optimization, adaptation, and individualization of drug treatments. The importance and costs of space missions require optimal health and safety measures to be implemented to ensure the health and performance of crews, both during and after missions.

Ethics statement

This review did not require ethical approval.

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CRediT authorship contribution statement

Audrey Derobertmasure: Writing – review & editing, Writing – original draft, Supervision, Project administration, Conceptualization. **Li Shean Toh:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Conceptualization. **Virginia E Wotring:** Writing – review & editing. **Philip M Williams:** Writing – review & editing. **Lucia Morbidelli:** Writing – review & editing. **Julia C Stingl:** Writing – review & editing. **Mathieu Vinken:** Writing – review & editing. **Raghda Ramadan:** Writing – review & editing. **Stephanie Chhun:** Writing – review & editing, Writing – original draft, Supervision, Conceptualization. **Pierre Boutouyrie:** Writing – review & editing, Writing – original draft, Supervision, Conceptualization.

Declaration of Competing Interest

The authors declare no competing interests.

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Data availability

The original contributions of this study are included in the article. Further inquiries can be directed to the corresponding author.

References

Aartsma-Rus, A., van Putten, M., 2019. The use of genetically humanized animal models for personalized medicine approaches. Dis. Model. Mech. 13 (2), dmm041673. https://doi.org/10.1242/dmm.041673.

Afshinnekoo, E., Scott, R.T., MacKay, M.J., et al., 2020. Fundamental biological features of spaceflight: advancing the field to enable deep-space exploration. Cell 183 (5), 1162–1184. https://doi.org/10.1016/j.cell.2020.10.050.

Agarwal, N., Rice, S.P.L., Bolusani, H., et al., 2010. Metformin reduces arterial stiffness and improves endothelial function in young women with polycystic ovary syndrome: a randomized, placebo-controlled, crossover trial. J. Clin. Endocrinol. Metab. 95 (2), 722–730. https://doi.org/10.1210/jc.2009-1985.

Alivon, M., Vo-Duc Phuong, T., Vignon, V., et al., 2015. A novel device for measuring arterial stiffness using finger-toe pulse wave velocity: validation study of the pOpmètre®. Arch. Cardiovasc. Dis. 108 (4), 227–234. https://doi.org/10.1016/j.acvd.2014.12.003.

Alqahtani, A.A., Ahmed, M.M., Mohammed, A.A., Ahmad, J., 2023. 3D Printed pharmaceutical systems for personalized treatment in metabolic syndrome. Pharmaceutics. 15 (4), 1152. https://doi.org/10.3390/pharmaceutics15041152.

Annaratone, L., De Palma, G., Bonizzi, G., et al., 2021. Basic principles of biobanking: from biological samples to precision medicine for patients. Virchows Arch. 479 (2), 233–246. https://doi.org/10.1007/s00428-021-03151-0.

Antonsen, E.L., Myers, J.G., Boley, L., et al., 2022. Estimating medical risk in human spaceflight. NPJ. Microgravity. 8 (1), 1–10. https://doi.org/10.1038/s41526-022-00193-9.

Auñón-Chancellor, S.M., Pattarini, J.M., Moll, S., Sargsyan, A., 2020. Venous thrombosis during spaceflight. N. Engl. J. Med. 382 (1), 89–90. https://doi.org/10.1056/NEJMc1905875.

Bácskay, I., Ujhelyi, Z., Fehér, P., Arany, P., 2022. The evolution of the 3D-printed drug delivery systems: A review. Pharmaceutics. 14 (7), 1312. https://doi.org/10.3390/pharmaceutics14071312.

Bakris, G.L., Saxena, M., Gupta, A., Chalhoub, F., et, Al., 2024. RNA interference with Zilebesiran for mild to moderate hypertension: the KARDIA-1 randomized clinical trial. JAMa 331, 740. https://doi.org/10.1001/jama.2024.0728.

Barinda, A.J., Hardi, H., Louisa, M., et al., 2024. Repurposing effect of cardiovascular-metabolic drug to increase lifespan: a systematic review of animal studies and current clinical trial progress. Front. Pharmacol. 15. https://doi.org/10.3389/fphar.2024.1373458.

Bauser HC, Smith PA, Parent SD, et al. Return of the Ritonavir: A study on the stability of pharmaceuticals processed in orbit. Published online March 19, 2024. doi:10.26434/chemrxiv-2024-vb20g.

Beheshti, A., Chakravarty, K., Fogle, H., et al., 2019. Multi-omics analysis of multiple missions to space reveal a theme of lipid dysregulation in mouse liver. Sci. Rep. 9 (1), 19195. https://doi.org/10.1038/s41598-019-55869-2.

Beierle, I., Meibohm, B., Derendorf, H., 1999. Gender differences in pharmacokinetics and pharmacodynamics. Int. J. Clin. Pharmacol. Ther. 37 (11), 529–547.

Belzile-Dugas, E., Eisenberg, MJ., 2021. Radiation-induced cardiovascular disease: review of an underrecognized pathology. J. Am. Heart. Assoc. 10 (18), e021686. https://doi.org/10.1161/JAHA.121.021686.

Bergouignan, A., Stein, T.P., Habold, C., Coxam, V., O' Gorman, D., Blanc, S., 2016. Towards human exploration of space: the THESEUS review series on nutrition and metabolism research priorities. NPJ. Microgravity. 2, 16029. https://doi.org/10.1038/npjmgrav.2016.29.

Bhatt, D.L., Steg, P.G., Miller, M., et al., 2019. Cardiovascular risk reduction with icosapent ethyl for hypertriglyceridemia. N. Engl. J. Med. 380 (1), 11–22. https://doi.org/10.1056/NEJMoa1812792.

Bio-Monitor, Agency CS., 2014. Keeping an eye on astronauts' vital signs. Canadian Space Agency. January 22,Accessed July 10, 2024. https://www.asc-csa.gc.ca/eng/sciences/bio-monitor.asp.

Boutouyrie, P., Chowienczyk, P., Humphrey, J.D., Mitchell, GF., 2021. Arterial stiffness and cardiovascular risk in hypertension. Circulat. Res. 128 (7), 864–886. https://doi.org/10.1161/CIRCRESAHA.121.318061.

Boutouyrie P, Derobermasure A, Morbidelli L, Raghda R, Toh LS, Stingl J, et al. White paper . White paper #14: pharmacological countermeasures. In: Agency ES, editor.: European SciSpace Roadmap; 2021. https://esamultimedia.esa.int/docs/HRE/14_HumanResearch_PharmacologicalCountermeasures.pdf.

Boutouyrie, P., Fayol, A., Fortier, C., et al., 2022. Impact of 60 days of head-down bed rest on large arteries. J. Hypertens. 40 (10), 2058–2067. https://doi.org/10.1097/HJH.0000000000003235.

Boyd JL, Wang Z, Putcha L. Bioavailability of promethazine during spaceflight. In:; 2009. Accessed December 21, 2021. https://ntrs.nasa.gov/citations/20090001322.

Buchheim, J.I., Matzel, S., Rykova, M., et al., 2019. Stress related shift toward inflammaging in cosmonauts after long-duration space flight. Front. Physiol. 10, 85. https://doi.org/10.3389/fphys.2019.00085.

Camera, A., Tabetah, M., Castañeda, V., et al., 2024. Aging and putative frailty biomarkers are altered by spaceflight. Sci. Rep. 14 (1), 13098. https://doi.org/10.1038/s41598-024-57948-5.

Campbell, T.J., Williams, KM., 1998. Therapeutic drug monitoring: antiarrhythmic drugs. Br. J. Clin. Pharmacol. 46 (4), 307–319. https://doi.org/10.1046/j.1365-2125.1998.t01-1-00768.x.

Campo del, L.S.D., Rodrigues-Díez, R., Salaices, M., Briones, A.M., García-Redondo, A.B., 2022. Specialized pro-resolving lipid mediators: new therapeutic approaches for vascular remodeling. Int. J. Mol. Sci. 23 (7). https://doi.org/10.3390/ijms23073592.

Carr, D.F., Francis, B., Jorgensen, A.L., et al., 2019. Genomewide Association study of statin-induced myopathy in patients recruited using the UK clinical practice research datalink. Clin. Pharmacol. Ther. 106 (6), 1353–1361. https://doi.org/10.1002/cpt.1557.

Casassus, B., 2018. Risks of reformulation: French patients complain after Merck modifies levothyroxine pills. BMJ k714. https://doi.org/10.1136/bmj.k714.

Chancellor, J.C., Scott, G.B.I., Sutton, JP., 2014. Space radiation: the number one risk to astronaut health beyond low Earth orbit. Life (Basel) 4 (3), 491–510. https://doi.org/10.3390/life4030491.

Chen, R., Wang, Y., Zhang, S., et al., 2023. Biomarkers of ageing: current state-of-art, challenges, and opportunities. MedComm – Future Med. 2 (2), e50. https://doi.org/10.1002/mef2.50.

Cho, C.K., Kang, P., Jang, C.G., Lee, S.Y., Lee, Y.J., Choi, CI., 2023. Physiologically based pharmacokinetic (PBPK) modeling to predict the pharmacokinetics of irbesartan in different CYP2C9 genotypes. Arch. Pharm. Res. 46 (11-12), 939–953. https://doi.org/10.1007/s12272-023-01472-z.

Cintron, N.M., Putcha, L., Parise, C., 1987. In-flight pharmacokinetics of acetaminophen in saliva. Results Life Sci. DSOs Cond. Aboard Space Shuttle. https://ntrs.nasa.gov/api/citations/19870017063/downloads/19870017063.pdf.

Climie, R.E., van Sloten, T.T., Bruno, R.M., et al., 2019. Macrovasculature and microvasculature at the crossroads between type 2 diabetes mellitus and hypertension. Hypertension 73 (6), 1138–1149. https://doi.org/10.1161/HYPERTENSIONAHA.118.11769.

Committee on the Peaceful Uses of Outer Space & Scientific and Technical Subcommittee. Annex III draft report of the Working Group on Space and Global Health. Published online 2022. https://www.unoosa.org/documents/pdf/copuos/stsc/gh/WG_report_2019.pdf).

Comstock, G.M., Fleischer, R.L., Giard, W.R., Hart, H.R., Nichols, G.E., Price, PB., 1971. Cosmic-ray tracks in plastics: the apollo helmet dosimetry experiment. Science (1979) 172 (3979), 154–157. https://doi.org/10.1126/science.172.3979.154.

Concordet, D., Gandia, P., Montastruc, J.L., et al., 2019. Levothyrox® new and old formulations: are they switchable for millions of patients? Clin. Pharmacokinet. 58 (7), 827–833. https://doi.org/10.1007/s40262-019-00747-3.

Corlett, T., Stavnichuk, M., Komarova, SV., 2020. Population analysis of space travelers. Life Sci. Space Res. (Amst) 27, 1–5. https://doi.org/10.1016/j.lssr.2020.06.003.

Cortese, F., Klokov, D., Osipov, A., et al., 2018. Vive la radiorésistance!: converging research in radiobiology and biogerontology to enhance human radioresistance for deep space exploration and colonization. Oncotarget. 9 (18), 14692–14722. https://doi.org/10.18632/oncotarget.24461.

COSMOS | Cardiovascular monitoring + pharmacology on Mars. TRANSATLANTIC MARS | CREW 261. Accessed July 10, 2024. https://www.transatlanticmarscrew261.com/experiments-1/cosmos.

Csiszar, A., Tarantini, S., Yabluchanskiy, A., Ungvari, Z., 2024. PCSK9: an emerging player in cardiometabolic aging and its potential as a therapeutic target and biomarker. Geroscience 46 (1), 257–263. https://doi.org/10.1007/s11357-023-01003-0.

Custaud, Marc-Antoine, Blanc, Stephane, Gauquelin-Koch, Guillemette, Gharib, Claude, 2020. L'humain et l'espace ; Ses Adaptations Physiologiques. Librairie Gallimard Paris.

Daniels VR, Williams ES. Exploring the complexities of drug formulation selection, storage, and shelf-life for exploration spaceflight. *Br. J. Clin. Pharmacol.*. doi:10.1111/bcp.15957.

Dash, R.P., Veeravalli, V., Thomas, J.A., Rosenfeld, C., Mehta, N., Srinivas, NR., 2021. Whole blood or plasma: what is the ideal matrix for pharmacokinetic-driven drug candidate selection? Future Med. Chem. 13 (2), 157–171. https://doi.org/10.4155/fmc-2020-0187.

da Silveira, W.A., Fazelinia, H., Rosenthal, S.B., et al., 2020. Comprehensive multi-omics analysis reveals mitochondrial stress as a Central biological hub for spaceflight impact. Cell 183 (5), 1185–1201. https://doi.org/10.1016/j.cell.2020.11.002 e20.

Davido, B., Michelon, H., Mamona, C., de Truchis, P., Jaffal, K., Saleh-Mghir, A., 2024. Efficacy of expired antibiotics: A real debate in the context of repeated drug shortages. Antibiotics. (Basel) 13 (5), 466. https://doi.org/10.3390/antibiotics13050466.

de Almeida, AJPO, de Almeida Rezende, M.S., Dantas, S.H., et al., 2020. Unveiling the role of inflammation and oxidative stress on age-related cardiovascular diseases. Oxid. Med. Cell Longev. 2020, 1954398. https://doi.org/10.1155/2020/1954398.

Deepika, D., Kumar, V., 2023. The role of "physiologically based pharmacokinetic model (PBPK)" new approach methodology (NAM) in pharmaceuticals and environmental chemical risk assessment. Int. J. Environ. Res. Public Health 20 (4), 3473. https://doi.org/10.3390/ijerph20043473.

Dello Russo, C., Bandiera, T., Monici, M., et al., 2022. Physiological adaptations affecting drug pharmacokinetics in space: what do we really know? A critical review of the literature. Br. J. Pharmacol. 179 (11), 2538–2557. https://doi.org/10.1111/bph.15822.

Delp, M.D., Charvat, J.M., Limoli, C.L., Globus, R.K., Ghosh, P., 2016. Apollo lunar astronauts show higher cardiovascular disease mortality: possible deep space radiation effects on the vascular endothelium. Sci. Rep. 6 (1), 1–11. https://doi.org/10.1038/srep29901.

Demeester, C., Robins, D., Edwina, A.E., et al., 2023. Physiologically based pharmacokinetic (PBPK) modelling of oral drug absorption in older adults - an AGePOP review. Eur. J. Pharm. Sci. 188, 106496. https://doi.org/10.1016/j.ejps.2023.106496.

Derache F, Thevenon A. IAF/IAA SPACE LIFE SCIENCES SYMPOSIUM (A1) medical care for humans in space (3). https://iafastro.directory/iac/paper/id/72079/abstract-pdf/IAC-22,A1,3,2,x72079.brief.pdf?2022-04-05.14:39:54.

Derobertmasure, A., Kably, B., Justin, J., De Sousa Carvalho, C., Billaud, E.M., Boutouyrie, P., 2023. Dried urine spot analysis for assessing cardiovascular drugs exposure applicable in spaceflight conditions. J. Chromatogr. B Analyt. Technol. Biomed. Life Sci. 1219, 123539. https://doi.org/10.1016/j.jchromb.2022.123539.

Derobertmasure, A., Toh, L.S., Kafi, L., Obeid, H., Burk, J., Decadi, A., et al., 2025. Exploring cardiovascular health and alternative biological fluid sampling methods in extreme environments: lessons from a 12-day Mars analog mission. Acta Astronaut. in press.

Derobertmasure, A., Toh, L.S., Verstuyft, C., Lukic, S., De Sousa Carvalho, C., Couronné, R., Beauvalet, M., Chhun, S., Boutouyrie, P., 2024. Feasibility of dried blood spot collection for caffeine pharmacokinetic studies in microgravity: insights from parabolic flight campaigns. Brit J Clin. Pharma bcp 16320. https://doi.org/10.1111/bcp.16320.

Desai, A.S., Webb, D.J., Taubel, J., et al., 2023. Zilebesiran, an RNA interference therapeutic agent for hypertension. N. Engl. J. Med. 389 (3), 228–238. https://doi.org/10.1056/NEJMoa2208391.

Desai, A.S., Webb, D.J., Taubel, J., Casey, S., Cheng, Y., Robbie, G.J., et al., 2023 Jul 20. Zilebesiran, an RNA interference therapeutic agent for hypertension. N. Engl. J. Med. 389 (3), 228–238. https://www.nejm.org/doi/full/10.1056/NEJMoa2208391.

Du, B., Daniels, V.R., Vaksman, Z., Boyd, J.L., Crady, C., Putcha, L., 2011. Evaluation of physical and chemical changes in pharmaceuticals flown on space missions. AAPS. J. 13 (2), 299–308. https://doi.org/10.1208/s12248-011-9270-0.

Du, B., Daniels, V.R., Vaksman, Z., Boyd, J.L., Crady, C., Putcha, L., 2011. Evaluation of physical and chemical changes in pharmaceuticals flown on space missions. AAPS. J. 13 (2), 299–308. https://doi.org/10.1208/s12248-011-9270-0.

Durante, W., Behnammanesh, G., Peyton, K.J., 2021. Effects of sodium-glucose Co-transporter 2 inhibitors on vascular cell function and arterial remodeling. Int. J. Mol. Sci. 22 (16), 8786. https://doi.org/10.3390/ijms22168786.

Eyal, S., Derendorf, H., 2019. Medications in space: In search of a pharmacologist's guide to the galaxy. Pharm. Res. 36 (10), 148. https://doi.org/10.1007/s11095-019-2679-3.

Eyal, S., 2020. How do the pharmacokinetics of drugs change in astronauts in space? Expert. Opin. Drug Metab. Toxicol. 0 (0), 1–4. https://doi.org/10.1080/17425255.2020.1746763.

FDA biomarkers politics. FDA. February 4, 2025. Accessed February 4, 2025. https://www.fda.gov/drugs/drug-development-tool-ddt-qualification-programs/biomarker-qualification-program.

Feldman, S., Brunner, LJ., 1994. Small animal model of weightlessness for pharmacokinetic evaluation. J. Clin. Pharmacol. 34 (6), 677–683. https://doi.org/10.1002/j.1552-4604.1994.tb02023.x.

Fleischer, R.L., Hart, H.R., Comstock, G.M., Carter, M., Renshaw, A., Hardy, A., 1973. Apollo 14 and Apollo 16 heavy-particle dosimetry experiments. Science (1979) 181 (4098), 436–438. https://doi.org/10.1126/science.181.4098.436.

Fletcher, C.V., Acosta, E.P., Strykowski, JM., 1994. Gender differences in human pharmacokinetics and pharmacodynamics. J. Adolesc. Health 15 (8), 619–629. https://doi.org/10.1016/s1054-139x(94)90628-9.

Fritsch, J.M., Charles, J.B., Bennett, B.S., Jones, M.M., Eckberg, DL., 1992. Short-duration spaceflight impairs human carotid baroreceptor-cardiac reflex responses. J. Appl. Physiol. (1985) 73 (2), 664–671. https://doi.org/10.1152/jappl.1992.73.2.664.

Gandia, P., Bareille, M.P., Saivin, S., et al., 2003. Influence of simulated weightlessness on the oral pharmacokinetics of acetaminophen as a gastric emptying probe in man: a plasma and a saliva study. J. Clin. Pharmacol. 43 (11), 1235–1243. https://doi.org/10.1177/0091270003257229.

Gandia, P., Saivin, S., Le-Traon, A.P., Guell, A., Houin, G., 2006. Influence of simulated weightlessness on the intramuscular and oral pharmacokinetics of promethazine in 12 human volunteers. J. Clin. Pharmacol. 46 (9), 1008–1016. https://doi.org/10.1177/0091270006291032.

Gandia, P., 2003. Influence of siSmulated weightlessness on the oral pharmacokinetics of acetaminophen as a gastric emptying probe in man: a plasma and a saliva study. J. Clin. Pharmacol. 43, 1235–1243.

Gao, R., Chilibeck, PD., 2020. Nutritional interventions during bed rest and spaceflight: prevention of muscle mass and strength loss, bone resorption, glucose intolerance, and cardiovascular problems. Nutr. Res. 82, 11–24. https://doi.org/10.1016/j.nutres.2020.07.001.

Garrett-Bakelman, F.E., Darshi, M., Green, S.J., et al., 2019. The NASA Twins Study: A multidimensional analysis of a year-long human spaceflight. Science (1979) 364 (6436). https://doi.org/10.1126/science.aau8650.

Gertz, M.L., Chin, C.R., Tomoiaga, D., et al., 2020. Multi-omic, single-cell, and biochemical profiles of astronauts guide pharmacological strategies for returning to gravity. Cell Rep. 33 (10). https://doi.org/10.1016/j.celrep.2020.108429.

Goetz, L.H., Schork, NJ., 2018. Personalized medicine: motivation, challenges and progress. Fertil. Steril. 109 (6), 952–963. https://doi.org/10.1016/j.fertnstert.2018.05.006.

Goldermann, M., Hanke, W., 2001. Ion channel are sensitive to gravity changes. Microgravity. Sci. Technol. 13 (1), 35–38. https://doi.org/10.1007/bf02873330.

Goldstein, R.H., Walensky, RP., 2019. Where were the women? Gender parity in clinical trials. N. Engl. J. Med. 381 (26), 2491–2493. https://doi.org/10.1056/NEJMp1913547.

Graebe, A., Schuck, E.L., Lensing, P., Putcha, L., Derendorf, H., 2004. Physiological, pharmacokinetic, and pharmacodynamic changes in space. J. Clin. Pharmacol. 44 (8), 837–853. https://doi.org/10.1177/0091270004267193.

Guerra Valero, Y., 2021. Microsampling to support pharmacokinetic clinical studies in pediatrics. Pediatr. Res. https://doi.org/10.1038/s41390-021-01586-4. Published online.

Hand, A.R., Dagdeviren, D., Larson, N.A., Haxhi, C., Mednieks, MI., 2020. Effects of spaceflight on the mouse submandibular gland. Arch. Oral Biol. 110, 104621. https://doi.org/10.1016/j.archoralbio.2019.104621.

Hargens, A.R., Vico, L., 2016. Long-duration bed rest as an analog to microgravity. J. Appl. Physiol. 120 (8), 891–903. https://doi.org/10.1152/japplphysiol.00935.2015.

Hicks, J., Olson, M., Mitchell, C., Juran, C.M., Paul, A.M., 2023. The impact of microgravity on immunological states. Immunohorizons. 7 (10), 670–682. https://doi.org/10.4049/immunohorizons.2200063.

Horton, W.B., Barrett, EJ., 2021. Microvascular dysfunction in diabetes mellitus and cardiometabolic disease. Endocr. Rev. 42 (1), 29–55. https://doi.org/10.1210/endrev/bnaa025.

Howard, J.P., Wood, F.A., Finegold, J.A., et al., 2021. Side effect patterns in a crossover trial of statin, Placebo, and No treatment. J. Am. Coll. Cardiol. 78 (12), 1210–1222. https://doi.org/10.1016/j.jacc.2021.07.022.

Hughson, R.L., Helm, A., Durante, M., 2018. Heart in space: effect of the extraterrestrial environment on the cardiovascular system. Nat. Rev. Cardiol. 15 (3), 167–180. https://doi.org/10.1038/nrcardio.2017.157.

Hughson, R.L., Helm, A., Durante, M., 2018. Heart in space: effect of the extraterrestrial environment on the cardiovascular system. Nat. Rev. Cardiol. 15 (3), 167–180. https://doi.org/10.1038/nrcardio.2017.157.

Hughson, RL., 2016. Increased postflight carotid artery stiffness and inflight insulin resistance resulting from 6-mo spaceflight in male and female astronauts. Am. J. Physiol-Heart Circulat. Physiol. 310, 628–H638.

Hwang, C., Lee, W.J., Kim, S.D., Park, S., Kim, JH., 2022. Recent advances in biosensor technologies for point-of-care urinalysis. Biosensors. (Basel) 12 (11), 1020. https://doi.org/10.3390/bios12111020.

Islam, M.M., Iqbal, U., Walther, B.A., et al., 2017. Gender-based personalized pharmacotherapy: a systematic review. Arch. Gynecol. Obstet. 295 (6), 1305–1317. https://doi.org/10.1007/s00404-017-4363-3.

Jain, V., Wotring, VE., 2016. Medically induced amenorrhea in female astronauts. NPJ. Microgravity. 2 (1), 1–6. https://doi.org/10.1038/npjmgrav.2016.8.

Jo, S.J., Chae, S.U., Lee, C.B., Bae, S.K. IJMS | Free full-text | clinical pharmacokinetics of approved RNA therapeutics. Accessed July 10, 2024. https://www.mdpi.com/1422-0067/24/1/746. 2023.

James JT, Kahn-Mayberry N. Risk of adverse health effects from lunar dust exposure. The Hum. Res. Progr. Evid. Book, NASA-SP-2009-3045. https://humanresearchroadmap.nasa.gov/Evidence/reports/Lunar%20Dust.pdf.

Janić, M., Lunder, M., Sabovič, M., 2014. Arterial stiffness and cardiovascular therapy. Biomed. Res. Int. 2014, 621437. https://doi.org/10.1155/2014/621437.

Jonscher, K.R., Alfonso-Garcia, A., Suhalim, J.L., et al., 2016. Spaceflight activates lipotoxic pathways in mouse liver. PLoS. One 11 (4), e0152877. https://doi.org/10.1371/journal.pone.0152877.

Kamali, F., Fry, J.R., Bell, GD., 1987. Salivary secretion of paracetamol in man. J. Pharm. Pharmacol. 39 (2), 150–152. https://doi.org/10.1111/j.2042-7158.1987.tb06967.x.

Kashuba, A.D., Nafziger, AN., 1998. Physiological changes during the menstrual cycle and their effects on the pharmacokinetics and pharmacodynamics of drugs. Clin.

Pharmacokinet. 34 (3), 203–218. https://doi.org/10.2165/00003088-199834030-00003.
Kasichayanula, S., Grover, A., Emery, M.G., et al., 2018. Clinical pharmacokinetics and pharmacodynamics of Evolocumab, a PCSK9 inhibitor. Clin. Pharmacokinet. 57 (7), 769–779. https://doi.org/10.1007/s40262-017-0620-7.
Kast, J., Yu, Y., Seubert, C.N., Wotring, V.E., Derendorf, H., 2017. Drugs in space: pharmacokinetics and pharmacodynamics in astronauts. Eur. J. Pharm. Sci. https://doi.org/10.1016/j.ejps.2017.05.025, 109S:S2-S8.
Katakam, P., Bhavaraju, M.L.R., Narayana, T.V., et al., 2024. Navigating the challenges of 3D printing personalized medicine in space explorations: A comprehensive review. Crit. Rev. Ther. Drug Carrier Syst. 41 (6), 89–110. https://doi.org/10.1615/CritRevTherDrugCarrierSyst.2024051126.
Kates, R.E., Harapat, S.R., Keefe, D.L., Goldwater, D., Harrison, DC., 1980. Influence of prolonged recumbency on drug disposition. Clin. Pharmacol. Ther. 28 (5), 624–628. https://doi.org/10.1038/clpt.1980.213.
Katsoulakis, E., Wang, Q., Wu, H., et al., 2024. Digital twins for health: a scoping review. NPJ. Digit. Med. 7 (1), 1–11. https://doi.org/10.1038/s41746-024-01073-0.
Khaled, S.A., Burley, J.C., Alexander, M.R., Yang, J., Roberts, CJ., 2015. 3D printing of five-in-one dose combination polypill with defined immediate and sustained release profiles. J. Control Release 217, 308–314. https://doi.org/10.1016/j.jconrel.2015.09.028.
Kim, J., Yang, G., Kim, Y., Kim, J., Ha, J., 2016. AMPK activators: mechanisms of action and physiological activities. Exp. Mol. Med. 48 (4). https://doi.org/10.1038/emm.2016.16 e224-e224.
Kinkorová, J., 2016. Biobanks in the era of personalized medicine: objectives, challenges, and innovation. EPMa J. 7 (1), 4. https://doi.org/10.1186/s13167-016-0053-7.
Kohn, F.P.M., Hauslage, J., 2019. The gravity dependence of pharmacodynamics: the integration of lidocaine into membranes in microgravity. NPJ. Microgravity. 5 (1), 1–6. https://doi.org/10.1038/s41526-019-0064-5.
Kostis, J.B., Packer, M., Black, H.R., Schmieder, R., Henry, D., Levy, E., 2004. Omapatrilat and enalapril in patients with hypertension: the Omapatrilat Cardiovascular Treatment vs. Enalapril (OCTAVE) trial*. Am. J. Hypertens. 17 (2), 103–111. https://doi.org/10.1016/j.amjhyper.2003.09.014.
Kovachevich, Irina, Putcha, Lakshmi. Physiologic alterations and pharmacokinetic changes during space flight. NSLP-NASA LIFE SCIENCES PORTAL. Accessed September 3, 2024. https://nlsp.nasa.gov/view/lsdapub/lsda_experiment/61d6489b-b520-51ae-80ee-15dbeac0c9e1.
Kovachevich, I.V., Kondratenko, S.N., Starodubtsev, A.K., Repenkova, LG., 2009. Pharmacokinetics of acetaminophen administered in tablets and capsules under long-term space flight conditions. Pharm. Chem. J. 43 (3), 130–133. https://doi.org/10.1007/s11094-009-0255-6.
Lacolley, P., Regnault, V., Segers, P., Laurent, S., 2017. Vascular smooth muscle cells and arterial stiffening: relevance in development, aging, and disease. Physiol. Rev. 97 (4), 1555–1617. https://doi.org/10.1152/physrev.00003.2017.
Lambadiari, V., Pavlidis, G., Kousathana, F., et al., 2018. Effects of 6-month treatment with the glucagon like peptide-1 analogue liraglutide on arterial stiffness, left ventricular myocardial deformation and oxidative stress in subjects with newly diagnosed type 2 diabetes. Cardiovasc. Diabetol. 17, 8. https://doi.org/10.1186/s12933-017-0646-z.
Langell, J., Jennings, R., Clark, J., Ward, JB., 2008. Pharmacological agents for the prevention and treatment of toxic radiation exposure in spaceflight. Aviat. Space Environ. Med. 79 (7), 651–660. https://doi.org/10.3357/asem.2113.2008.
Laurent, S., Chatellier, G., Azizi, M., et al., 2021. SPARTE Study: normalization of arterial stiffness and cardiovascular events in patients with hypertension at medium to very high risk. Hypertension 78 (4), 983–995. https://doi.org/10.1161/HYPERTENSIONAHA.121.17579.
Laurent, S., 2021. SPARTE Study: normalization of arterial stiffness and cardiovascular events in patients with hypertension at medium to very high risk. Hypertension 78, 983–995.
Law, J., PaulB, Macbeth, 2011. Ultrasound: from Earth to space. Mcgill. J. Med. 13 (2), 59. Accessed July 10, 2024. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3296555/.
Lechat, P., 2022. Interchangeability between generic and reference products: limits of average bioequivalence methodology. Eur. J. Drug Metab. Pharmacokinet. 47 (6), 777–787. https://doi.org/10.1007/s13318-022-00785-6.
Levy, G., 1967. Effect of bed rest on distribution and elimination of drugs. J. Pharm. Sci. 56 (7), 928–929. https://doi.org/10.1002/jps.2600560739.
Li, D.F., Gao, Y.L., Liu, H.C., Huang, X.C., Zhu, R.F., Zhu, CT., 2020. Use of thiazide diuretics for the prevention of recurrent kidney calculi: a systematic review and meta-analysis. J. Transl. Med. 18 (1), 106. https://doi.org/10.1186/s12967-020-02270-7.
Liao, J.K., Laufs, U., 2005. Pleiotropic effects of statins. Annu. Rev. Pharmacol. Toxicol. 45, 89–118.
Liao, J.K., Laufs, U., 2005. Pleiotropic effects of statins. Annu. Rev. Pharmacol. Toxicol. 45, 89–118. https://doi.org/10.1146/annurev.pharmtox.45.120403.095748.
Marnat, M., 2022. EveryWear, a Human research and health mobile assistant for exploration. In: Proceedings of the International Astronautical Congress, IAC.. https://iafastro.directory/iac/paper/id/69181/abstract-pdf/IAC-22,A2,5,1,x69181.brief.pdf?2022-03-30.09:54:51.
Marshall-Goebel, K., Laurie, S.S., Alferova, I.V., et al., 2019. Assessment of jugular venous blood flow stasis and thrombosis during spaceflight. JAMa Netw. Open. 2 (11). https://doi.org/10.1001/jamanetworkopen.2019.15011 e1915011-e1915011.
Martina H., W.H. Paloski, et al., 2006. Space motion sickness: Incidence, etiology, and countermeasures, Auton Neurosci., 129(1–2), 2006. doi:10.1016/j.autneu.2006.07.014.
Mastrandrea, C.J., Hedge, E.T., Hughson, RL., 2024. The detrimental effects of bedrest: premature cardiovascular aging and dysfunction. Canad. J. Cardiol. https://doi.org/10.1016/j.cjca.2024.05.009. Published online May 15.
Mathur, S., Sutton, J., 2017. Personalized medicine could transform healthcare. Biomed. Rep. 7 (1), 3–5. https://doi.org/10.3892/br.2017.922.
Mathyk, B.A., Tabetah, M., Karim, R., et al., 2024. Spaceflight induces changes in gene expression profiles linked to insulin and estrogen. Commun. Biol. 7 (1), 1–17. https://doi.org/10.1038/s42003-023-05213-2.
Matyas, C., Trojnar, E., Zhao, S., et al., 2023. PCSK9, A promising novel target for age-related cardiovascular dysfunction. JACC: Basic Translat. Sci. 8 (10), 1334–1353. https://doi.org/10.1016/j.jacbts.2023.06.005.
Mayo, P.R., Skeith, K., Russell, A.S., Jamali, F., 2000. Decreased dromotropic response to verapamil despite pronounced increased drug concentration in rheumatoid arthritis. Br. J. Clin. Pharmacol. 50 (6), 605–613. https://doi.org/10.1046/j.1365-2125.2000.00314.x.
McLaughlin, M.F., Donoviel, D.B., Jones, JA., 2017. Novel indications for commonly used medications as radiation protectants in spaceflight. Aerosp. Med. Hum. Perform. 88 (7), 665–676. https://doi.org/10.3357/AMHP.4735.2017.
Medical-Grade Smartwatch Can Monitor Astronauts, Patients | NASA spinoff. Accessed July 10, 2024. https://spinoff.nasa.gov/Medical-Grade_Smartwatch_Can_Monitor_Astronauts_Patients.
Meerman, M., Bracco Gartner, T.C.L., Buikema, J.W., et al., 2021. Myocardial disease and long-distance space travel: solving the radiation problem. Front. Cardiovasc. Med. 8. https://doi.org/10.3389/fcvm.2021.631985.
Meibohm, B., Beierle, I., Derendorf, H., 2002. How important are gender differences in pharmacokinetics? Clin. Pharmacokinet. 41 (5), 329–342. https://doi.org/10.2165/00003088-200241050-00002.
Miranda, S., Marchal, S., Cumps, L., et al., 2023. A dusty road for astronauts. Biomedicines. 11 (7), 1921. https://doi.org/10.3390/biomedicines11071921.
Morbidelli, L., Genah, S., Cialdai, F., 2021. Effect of microgravity on endothelial cell function, angiogenesis, and vessel remodeling during wound healing. Front. Bioeng. Biotechnol. 9, 720091. https://doi.org/10.3389/fbioe.2021.720091.
Morgan, PE., 2021. Microsampling devices for routine therapeutic drug monitoring-are we there yet? Ther. Drug Monit. 43 (3), 322–334. https://doi.org/10.1097/FTD.0000000000000884.
Navasiolava, N., Yuan, M., Murphy, R., et al., 2020. Vascular and microvascular dysfunction induced by microgravity and its analogs in humans: mechanisms and countermeasures. Front. Physiol. 11, 952. https://doi.org/10.3389/fphys.2020.00952.
Navasiolava, N.M., Custaud, M.A., Tomilovskaya, E.S., et al., 2011. Long-term dry immersion: review and prospects. Eur. J. Appl. Physiol. 111 (7), 1235–1260. https://doi.org/10.1007/s00421-010-1750-x.
Norsk, P., 2020. Adaptation of the cardiovascular system to weightlessness: surprises, paradoxes and implications for deep space missions. Acta Physiol. (Oxf) 228 (3), e13434. https://doi.org/10.1111/apha.13434.
Obeid, H., Khettab, H., Marais, L., Hallab, M., Laurent, S., Boutouyrie, P., 2017. Evaluation of arterial stiffness by finger–toe pulse wave velocity: optimization of signal processing and clinical validation. J. Hypertens. 35 (8), 1618–1625. https://doi.org/10.1097/HJH.0000000000001371.
O'Donoghue, M.L., Rosenson, R.S., Gencer, B., et al., 2022. Small interfering RNA to reduce lipoprotein(a) in cardiovascular disease. N. Engl. J. Med. 387 (20), 1855–1864. https://doi.org/10.1056/NEJMoa2211023.
Olawi, N., Krüger, M., Grimm, D., Infanger, M., Wehland, M., 2019. Nebivolol in the treatment of arterial hypertension. Basic Clin. Pharmacol. Toxicol. 125 (3), 189–201. https://doi.org/10.1111/bcpt.13248.
Ouslimani, N., Peynet, J., Bonnefont-Rousselot, D., Thérond, P., Legrand, A., Beaudeux, JL., 2005. Metformin decreases intracellular production of reactive oxygen species in aortic endothelial cells. Metabolism. 54 (6), 829–834. https://doi.org/10.1016/j.metabol.2005.01.029.
Overbey, E.G., Kim, J., Tierney, B.T., et al., 2024. The Space Omics and Medical Atlas (SOMA) and international astronaut biobank. Nature 1–3. https://doi.org/10.1038/s41586-024-07639-y. Published online June 11.
Overbey, E.G., Ryon, K., Kim, J., et al., 2024. Collection of biospecimens from the inspiration4 mission establishes the standards for the space omics and medical atlas (SOMA). Nat. Commun. 15 (1), 4964. https://doi.org/10.1038/s41467-024-48806-z.
Paintaud, G., 2009. Pharmacocinétique des anticorps monoclonaux. Med. Sci. (Paris) 25 (12), 1057–1062. https://doi.org/10.1051/medsci/200925121057.
Paloschi, V., Sabater-Lleal, M., Middelkamp, H., et al., 2021. Organ-on-a-chip technology: a novel approach to investigate cardiovascular diseases. Cardiovasc. Res. 117 (14), 2742–2754. https://doi.org/10.1093/cvr/cvab088.
Panspermia - an overview | ScienceDirect topics. Accessed July 15, 2024. https://www.sciencedirect.com/topics/physics-and-astronomy/panspermia.
Paolino, S., Goegan, F., Cimmino, M.A., et al., 2020. Advanced microvascular damage associated with occurence of sarcopenia in systemic sclerosis patients: results from a retrospective cohort study. Clin. Exp. Rheumatol. 38 (3), 65–72. Suppl 125.
Paradies, G., Paradies, V., Ruggiero, F.M., Petrosillo, G., 2014. Oxidative stress, cardiolipin and mitochondrial dysfunction in nonalcoholic fatty liver disease. World J. Gastroenterol. 20 (39), 14205–14218. https://doi.org/10.3748/wjg.v20.i39.14205.
Patel, S., 2020. The effects of microgravity and space radiation on cardiovascular health: from low-Earth orbit and beyond. IJC Heart & Vasculature 30, 100595. https://doi.org/10.1016/j.ijcha.2020.100595.
Patel, S., 2020. The effects of microgravity and space radiation on cardiovascular health: from low-Earth orbit and beyond. IJC Heart Vasculature 30, 100595. https://doi.org/10.1016/j.ijcha.2020.100595.

Patel, Z.S., Brunstetter, T.J., Tarver, W.J., et al., 2020. Red risks for a journey to the red planet: the highest priority human health risks for a mission to Mars. NPJ. Microgravity. 6 (1), 1–13. https://doi.org/10.1038/s41526-020-00124-6.
Pavy-Le Traon, A., Heer, M., Narici, M.V., Rittweger, J., Vernikos, J., 2007. From space to Earth: advances in human physiology from 20 years of bed rest studies (1986-2006). Eur. J. Appl. Physiol. 101 (2), 143–194. https://doi.org/10.1007/s00421-007-0474-z.
Peeters, L.E.J., Bahmany, S., Dekker, T., et al., 2022. Development and validation of a dried blood spot assay using UHPLC-MS/MS to identify and quantify 12 antihypertensive drugs and 4 active metabolites: clinical needs and analytical limitations. Ther. Drug Monit. 44 (4), 568–577. https://doi.org/10.1097/FTD.0000000000000984.
Peeters, L.E.J., Feyz, L., Boersma, E., et al., 2020. Clinical applicability of monitoring antihypertensive drug levels in blood. Hypertension 76 (1), 80–86. https://doi.org/10.1161/HYPERTENSIONAHA.120.15038.
Peeters, L.E.J., Feyz, L., Hameli, E., et al., 2020. Clinical validation of a dried blood spot assay for 8 antihypertensive drugs and 4 active metabolites. Ther. Drug Monit. 42 (3), 460–467. https://doi.org/10.1097/FTD.0000000000000703.
Peeters, L.E.J., Kappers, M.H.W., Hesselink, D.A., et al., 2024. Antihypertensive drug concentration measurement combined with personalized feedback in resistant hypertension: a randomized controlled trial. J. Hypertens. 42 (1), 169–178. https://doi.org/10.1097/HJH.0000000000003585.
Perry, C., Davis, G., Conner, T.M., Zhang, T., 2020. Utilization of physiologically based pharmacokinetic modeling in clinical pharmacology and therapeutics: an overview. Curr. Pharmacol. Rep. 6 (3), 71–84. https://doi.org/10.1007/s40495-020-00212-x.
Polyakov, A.V., Svistunov, A.A., Kondratenko, S.N., et al., 2020. Peculiarities of pharmacokinetics and bioavailability of some cardiovascular drugs under conditions of antiorthostatic hypokinesia. Bull. Exp. Biol. Med. 168 (4), 465–469. https://doi.org/10.1007/s10517-020-04732-w.
Powers, J., Bernstein, D., 2004. The mouse as a model of cardiovascular adaptations to microgravity. J. Appl. Physiol. (1985) 97 (5), 1686–1692. https://doi.org/10.1152/japplphysiol.00925.2003.
Putcha, L., Berens, K.L., Marshburn, T.H., Ortega, H.J., Billica, RD., 1999. Pharmaceutical use by U.S. astronauts on space shuttle missions. Aviat. Space Environ. Med. 70 (7), 705–708.
Putcha, L., Cintrón, NM., 1991. Pharmacokinetic consequences of spaceflight. Ann. N. Y. Acad. Sci. 618, 615–618. https://doi.org/10.1111/j.1749-6632.1991.tb27292.x.
Ray, K.K., Landmesser, U., Leiter, L.A., et al., 2017. Inclisiran in patients at high cardiovascular risk with elevated LDL cholesterol. N. Engl. J. Med. 376 (15), 1430–1440. https://doi.org/10.1056/NEJMoa1615758.
Ray, K.K., Landmesser, U., Leiter, L.A., et al., 2017. Inclisiran in patients at high cardiovascular risk with elevated LDL cholesterol. N. Engl. J. Med. 376 (15), 1430–1440. https://doi.org/10.1056/NEJMoa1615758.
Rehnberg, E., Quaghebeur, K., Baselet, B., et al., 2023. Biomarkers for biosensors to monitor space-induced cardiovascular ageing. Front Sens 4. https://doi.org/10.3389/fsens.2023.1015403.
Reichard, J.F., Phelps, S.E., Lehnhardt, K.R., Young, M., Easter, BD., 2023. The effect of long-term spaceflight on drug potency and the risk of medication failure. NPJ. Microgravity. 9 (1), 35. https://doi.org/10.1038/s41526-023-00271-6.
Research C for DE and, 2022. Table of pharmacogenomic biomarkers in drug labeling. FDA. Published online November 8Accessed November 29, 2022. https://www.fda.gov/drugs/science-and-research-drugs/table-pharmacogenomic-biomarkers-drug-labeling.
Rifai, M.A., Ballantyne, CM., 2021. PCSK9-targeted therapies: present and future approaches. Nat. Rev. Cardiol. 18 (12), 805–806. https://doi.org/10.1038/s41569-021-00634-0.
Roshanravan, N., Ghaffari, S., Bastani, S., et al., 2023. Human cardiac organoids: A recent revolution in disease modeling and regenerative medicine. J. Cardiovasc. Thorac. Res. 15 (2), 68–72. https://doi.org/10.34172/jcvtr.2023.31830.
Rudwill, F., Bergouignan, A., Gastebois, C., et al., 2015. Effect of enforced physical inactivity induced by 60-day of bed rest on hepatic markers of NAFLD in healthy normal-weight women. Liver. Int. 35 (6), 1700–1706. https://doi.org/10.1111/liv.12743.
Saivin, S., Pavy-Le Traon, A., Cornac, A., Güell, A., Houin, G., 1995. Impact of a four-day head-down tilt (-6 degrees) on lidocaine pharmacokinetics used as probe to evaluate hepatic blood flow. J. Clin. Pharmacol. 35 (7), 697–704. https://doi.org/10.1002/j.1552-4604.1995.tb04110.x.
Sanaka, M., Kuyama, Y., Nishinakagawa, S., Mineshita, S., 2000. Use of salivary acetaminophen concentration to assess gastric emptying rate of liquids. J. Gastroenterol. 35 (6), 429–433. https://doi.org/10.1007/s005350070087.
Sanders, L.M., Scott, R.T., Yang, J.H., et al., 2023. Biological research and self-driving labs in deep space supported by artificial intelligence. Nat. Mach. Intell. 5 (3), 208–219. https://doi.org/10.1038/s42256-023-00618-4.
Sangkuhl, K., Claudio-Campos, K., Cavallari, L.H., et al., 2021. PharmVar GeneFocus: CYP2C9. Clin. Pharmacol. Ther. 110 (3), 662–676. https://doi.org/10.1002/cpt.2333.
Savoia, C., Volpe, M., Kreutz, R., 2021. Hypertension, a moving target in COVID-19: current views and perspectives. Circ. Res. 128 (7), 1062–1079. https://doi.org/10.1161/CIRCRESAHA.121.318054.
Sawyers, L., Anderson, C., Boyd, M.J., et al., 2022. Astropharmacy: pushing the boundaries of the pharmacists' role for sustainable space exploration. Res. Social. Adm. Pharm. https://doi.org/10.1016/j.sapharm.2022.02.002. Published online February 12S1551-7411(22)00034-1.
Scalzo, R.L., Moreau, K.L., Ozemek, C., et al., 2017. Exenatide improves diastolic function and attenuates arterial stiffness but does not alter exercise capacity in individuals with type 2 diabetes. J Diabetes Complicat. 31 (2), 449–455. https://doi.org/10.1016/j.jdiacomp.2016.10.003.
Schuck, E.L., Grant, M., Derendorf, H., 2005. Effect of simulated microgravity on the disposition and tissue penetration of ciprofloxacin in healthy volunteers. J. Clin. Pharmacol. 45 (7), 822–831. https://doi.org/10.1177/0091270005276620.
Scott, J.M., Downs, M., Martin, D.S., et al., 2021. Teleguided self-ultrasound scanning for longitudinal monitoring of muscle mass during spaceflight. iScience 24 (4), 102344. https://doi.org/10.1016/j.isci.2021.102344.
Scott, J.M., Stoudemire, J., Dolan, L., Downs, M., 2022. Leveraging spaceflight to advance cardiovascular research on earth. Circ. Res. 130 (6), 942. https://doi.org/10.1161/CIRCRESAHA.121.319843.
Scott RT, Antonsen EL, Sanders LM, et al. Beyond Low Earth Orbit: biomonitoring, artificial intelligence, and precision space health. Published online December 22, 2021. doi:10.48550/arXiv.2112.12554.
Scott, R.T., Sanders, L.M., Antonsen, E.L., et al., 2023. Biomonitoring and precision health in deep space supported by artificial intelligence. Nat. Mach. Intell. 5 (3), 196–207. https://doi.org/10.1038/s42256-023-00617-5.
Shakeri, A., Wang, Y., Zhao, Y., et al., 2023. Engineering organ-on-a-chip systems for vascular diseases. Arterioscler. Thromb. Vasc. Biol. 43 (12), 2241–2255. https://doi.org/10.1161/ATVBAHA.123.318233.
Shigiyama, F., Kumashiro, N., Miyagi, M., et al., 2017. Effectiveness of dapagliflozin on vascular endothelial function and glycemic control in patients with early-stage type 2 diabetes mellitus: DEFENCE study. Cardiovasc. Diabetol. 16, 84. https://doi.org/10.1186/s12933-017-0564-0.
Silveira, WA., 2020. Comprehensive multi-omics analysis reveals mitochondrial stress as a Central biological hub for spaceflight impact. Cell 183, 1185–1201, 20.
Smith, M., Whitehead, E., O'Sullivan, G., Reynolds, F., 1991. A comparison of serum and saliva paracetamol concentrations. Br. J. Clin. Pharmacol. 31 (5), 553–555. Accessed December 13, 2021. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1368476/.
Smith, S.M., Heer, M.A., Shackelford, L.C., Sibonga, J.D., Ploutz-Snyder, L., Zwart, SR., 2012. Benefits for bone from resistance exercise and nutrition in long-duration spaceflight: evidence from biochemistry and densitometry. J. Bone Miner. Res. 27 (9), 1896–1906. https://doi.org/10.1002/jbmr.1647.
Sörensen, BM., 2016. Prediabetes and type 2 diabetes are associated with generalized microvascular dysfunction: the Maastricht study. Circulation 134, 1339–1352.
Space omics and Medical Atlas (SOMA) across orbits. Nature, 2024. June 11,Accessed July 10, 2024. https://www.nature.com/collections/ebdbcahdgc.
Spooner, N., 2019. Microsampling: considerations for its use in pharmaceutical drug discovery and development. Bioanalysis. 11, 1015–1038.
Stanke-Labesque, F., Gautier-Veyret, E., Chhun, S., Guilhaumou, R., French Society of Pharmacology and Therapeutics, 2020. Inflammation is a major regulator of drug metabolizing enzymes and transporters: consequences for the personalization of drug treatment. Pharmacol. Ther. 215, 107627. https://doi.org/10.1016/j.pharmthera.2020.107627.
Stehouwer, CDA., 2018. Microvascular dysfunction and hyperglycemia: A vicious cycle with widespread consequences. Diabetes 67 (9), 1729–1741. https://doi.org/10.2337/dbi17-0044.
Stingl, J.C., Welker, S., Hartmann, G., Damann, V., Gerzer, R., 2015. Where failure is not an option –Personalized medicine in astronauts. PLoS. One 10 (10), e0140764. https://doi.org/10.1371/journal.pone.0140764.
Strangman, G.E., Sawyer, A., Fabre, K.M., et al., 2019. Deep-space applications for point-of-care technologies. Curr. Opin. Biomed. Eng. 11, 45–50. https://doi.org/10.1016/j.cobme.2019.08.014.
Sugiyama, S., Jinnouchi, H., Kurinami, N., et al., 2018. The SGLT2 inhibitor Dapagliflozin significantly improves the peripheral microvascular endothelial function in patients with uncontrolled type 2 diabetes mellitus. Intern. Med. 57 (15), 2147–2156. https://doi.org/10.2169/internalmedicine.0701-17.
Szafron, J.M., Heng, E.E., Boyd, J., Humphrey, J.D. and Marsden, A.L. Hemodynamics and wall mechanics of vascular graft failure | arteriosclerosis, thrombosis, and vascular biology. Accessed July 15, 2024. https://www.ahajournals.org/doi/10.1161/ATVBAHA.123.318239.
Tabury, K., Rehnberg, E., Baselet, B., Baatout, S., Moroni, L., 2023. Bioprinting of cardiac tissue in space: where are we? Adv. Healthc. Mater. 12 (23), e2203338. https://doi.org/10.1002/adhm.202203338.
Takahashi, I., Shimizu, Y., Grant, E.J., Cologne, J., Ozasa, K., Kodama, K., 2017. Heart disease mortality in the life span study, 1950-2008. Radiat. Res. 187 (3), 319–332. https://doi.org/10.1667/RR14347.1.
Tenreiro, M.F., Louro, A.F., Alves, P.M., Serra, M., 2021. Next generation of heart regenerative therapies: progress and promise of cardiac tissue engineering. NPJ. Regen. Med. 6 (1), 1–17. https://doi.org/10.1038/s41536-021-00140-4.
Tentolouris, A., Vlachakis, P., Tzeravini, E., Eleftheriadou, I., Tentolouris, N., 2019. SGLT2 Inhibitors: A review of their antidiabetic and cardioprotective effects. Int. J. Environ. Res. Public Health 16 (16), 2965. https://doi.org/10.3390/ijerph16162965.
Ternant, D., Chhun, S., 2019. Variabilité pharmacocinétique des anticorps thérapeutiques. Med. Sci. (Paris) 35 (12), 1130–1136. https://doi.org/10.1051/medsci/2019210.
Tey, H.Y., See, HH., 2021. A review of recent advances in microsampling techniques of biological fluids for therapeutic drug monitoring. J. Chromatogr. A 1635, 461731. https://doi.org/10.1016/j.chroma.2020.461731.
Thirsk, R., Kuipers, A., Mukai, C., Williams, D., 2009. The space-flight environment: the International Space Station and beyond. CMAJ. 180 (12), 1216–1220. https://doi.org/10.1503/cmaj.081125.
Tobin, B.W., Uchakin, P.N., Leeper-Woodford, SK., 2002. Insulin secretion and sensitivity in space flight: diabetogenic effects. Nutrition 18 (10), 842–848. https://doi.org/10.1016/S0899-9007(02)00940-1.

Toprak, C., Yigitaslan, S., 2019. Alagebrium and complications of diabetes mellitus. EurAsian J. Med. 51 (3), 285–292. https://doi.org/10.5152/eurasianjmed.2019.18434.

Valencia, W.M., Palacio, A., Tamariz, L., Florez, H., 2017. Metformin and ageing: improving ageing outcomes beyond glycaemic control. Diabetologia 60 (9), 1630–1638. https://doi.org/10.1007/s00125-017-4349-5.

Van Ombergen, A., Chalupa-Gantner, F., Chansoria, P., et al., 2023. 3D Bioprinting in microgravity: opportunities, challenges, and possible applications in space. Adv. Healthcare Mater. 12 (23), 2300443. https://doi.org/10.1002/adhm.202300443.

Versmissen J, van Steenkiste J, Koch BCP, Peeters LEJ. 'Under pressure': the role of therapeutic drug monitoring in the treatment of hypertension. *Br. J. Clin. Pharmacol.*. doi:10.1111/bcp.16125.

Vico, L., van Rietbergen, B., Vilayphiou, N., et al., 2017. Cortical and trabecular bone microstructure did not recover at weight-bearing skeletal sites and progressively deteriorated at non-weight-bearing sites during the year following International Space Station missions. J. Bone Miner. Res. 32 (10), 2010–2021. https://doi.org/10.1002/jbmr.3188.

Vinge, E., 1998. Men and women respond differently to drugs. Hormone-dependent pharmacodynamic differences are rarely studied]. Lakartidningen. 95 (28-29), 3177–3182.

Vinken M. Hepatology in space: effects of spaceflight and simulated microgravity on the liver. *Liver. Int.*. n/a(n/a). doi:10.1111/liv.15444.

Virtual Twins as tools for personalized clinical care. Accessed February 1, 2025. https://vital-horizoneurope.eu.

Wang, H., Ning, X., Zhao, F., Zhao, H., Li, D., 2024. Human organoids-on-chips for biomedical research and applications. Theranostics. 14 (2), 788–818. https://doi.org/10.7150/thno.90492.

Wang X, Yu F, Zheng WQ. Aldose reductase inhibitor Epalrestat alleviates high glucose-induced cardiomyocyte apoptosis via ROS. Eur. Rev. August 7, 2019. Accessed September 3, 2024. https://www.europeanreview.org/article/18660.

Wang, X., Yu, F., Zheng, W.-Q., 2019. Aldose reductase inhibitor Epalrestat alleviates high glucose-induced cardiomyocyte apoptosis via ROS. Eur. Rev. https://doi.org/10.26355/eurrev_201908_18660. August 7,Accessed April 11, 2022. https://www.europeanreview.org/article/18660.

Watenpaugh, DE., 2016. Analogs of microgravity: head-down tilt and water immersion. J. Appl. Physiol. 120 (8), 904–914. https://doi.org/10.1152/japplphysiol.00986.2015.

Weerts, A.P., Putcha, L., Hoag, S.W., et al., 2015. Intranasal scopolamine affects the semicircular canals centrally and peripherally. J. Appl. Physiol. 119 (3), 213–218. https://doi.org/10.1152/japplphysiol.00149.2015.

Welcome to AstroCardia | Space project to improve heart health. AstroCardia. Accessed July 10, 2024. https://astrocardia.com/.

Wiencek, J.R., Das, S., Beheshti, A., et al., 2023. Lab medicine in space. Clin. Chem. 69 (5), 442–449. https://doi.org/10.1093/clinchem/hvad035.

Williams, P.M., Shivakumar, T., Anyanwu, V., 2022. Space medicine and countermeasures. In-Space Manufacturing and Resources. John Wiley & Sons, Ltd, pp. 21–46. https://doi.org/10.1002/9783527830909.ch2.

Wotring, V.E., Smith, LK., 2020. Dose tracker application for collecting medication use data from International Space Station crew. Aerosp. Med. Hum. Perform. 91 (1), 41–45. https://doi.org/10.3357/AMHP.5392.2020.

Wotring, VE., 2012. Space Pharmacology. Springer Science & Business Media.

Wotring, VE., 2015. Medication use by U.S. crewmembers on the International Space Station. FASEB J. 29 (11), 4417–4423. https://doi.org/10.1096/fj.14-264838.

Wotring, VE., 2015. Medication use by U.S. crewmembers on the International Space Station. FASEB J. 29 (11), 4417–4423. https://doi.org/10.1096/fj.14-264838.

Wu, E.T., Liang, J.T., Wu, M.S., Chang, KC., 2011. Pyridoxamine prevents age-related aortic stiffening and vascular resistance in association with reduced collagen glycation. Exp. Gerontol. 46 (6), 482–488. https://doi.org/10.1016/j.exger.2011.02.001.

Xu, X., Robles-Martinez, P., Madla, C.M., et al., 2020. Stereolithography (SLA) 3D printing of an antihypertensive polyprintlet: case study of an unexpected photopolymer-drug reaction. Add. Manufact. 33, 101071. https://doi.org/10.1016/j.addma.2020.101071.

Yokoyama, M., Origasa, H., Matsuzaki, M., Matsuzawa, Y., Saito, Y., Ishikawa, Y., et al., 2007. Effects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS): a randomised open-label, blinded endpoint analysis. Lancet 369 (9567), 1090–1098. Mar 31.

Zamir, A., Rasool, M.F., Imran, I., et al., 2023. Physiologically based pharmacokinetic model to predict metoprolol disposition in healthy and disease populations. ACS. Omega 8 (32), 29302–29313. https://doi.org/10.1021/acsomega.3c02673.

Zanoli, L., Briet, M., Empana, J.P., et al., 2020. Vascular consequences of inflammation: a position statement from the ESH Working Group on Vascular Structure and Function and the ARTERY Society. J. Hypertens. 38 (9), 1682–1698. https://doi.org/10.1097/HJH.0000000000002508.

Zhang, J., Tecson, K.M., Rocha, N.A., McCullough, PA., 2018. Usefulness of alirocumab and evolocumab for the treatment of patients with diabetic dyslipidemia. Proc. (Bayl. Univ. Med. Cent) 31 (2), 180–184. https://doi.org/10.1080/08998280.2018.1441255.

Zhang, J., Wang, X., Fu, Z., et al., 2024. Long-term simulated microgravity fosters carotid aging-like changes via Piezo1. Cardiovasc. Res. 120 (5), 548–559. https://doi.org/10.1093/cvr/cvae024.

Zhao, Z., Chen, X., Dowbaj, A.M., et al., 2022. Organoids. Nat. Rev. Methods Primers. 2 (1), 1–21. https://doi.org/10.1038/s43586-022-00174-y.

Zheng, M., Charvat, J., Zwart, S.R., et al., 2023. Time-resolved molecular measurements reveal changes in astronauts during spaceflight. Front. Physiol. 14, 1219221. https://doi.org/10.3389/fphys.2023.1219221.