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Pharmaceutical and biomedical challenges for crew autonomy in health preservation during future exploration missions

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Human space missions beyond Low Earth Orbit (LEO), such as to the Moon and Mars, will require increased crew autonomy in health management, due to communication delays and limited resupply. These missions pose unique biomedical challenges, including radiation exposure, altered gravity, and prolonged isolation, which can affect physiology and compromise available treatments. This review examines current efforts in pharmaceutical and biomedical strategies to support health preservation during long-duration missions. We discuss technologies needed to assure drug stability and storage, also considering potential modifications of pharmacokinetics in space, and the potential of nanotechnologies, physical therapies, and *in-situ* manufacturing. Non-pharmacological tools for diagnostics, trauma care, and tissue regeneration are highlighted for their promise in enhancing medical self-sufficiency. These advances are not only critical for ensuring mission success and crew safety beyond LEO, yet may also translate to healthcare solutions in remote or underserved Earth settings.

Space agencies are taking steps to enter a new era of exploration, pushing the boundaries of human exploration beyond the Low Earth Orbit (LEO). The roadmap defined by the International Space Exploration Coordination Group[1–3] for human exploration of deep space has as its ultimate goal the colonization of Mars and identifies the construction of stable bases on the Moon as an intermediate phase.

The International Space Station (ISS) experience reveals that permanence in space represents a major challenge to living organisms due to the large variety of stressors that can negatively affect them. The beyond-LEO mission scenario is even more challenging than that of the ISS and entails unique biological and biomedical concerns never faced before and that need to be resolved. Whereas within LEO, the Earth's magnetosphere plays a protective role for the crewmembers, the upcoming exploration missions will expose astronauts to increased galactic cosmic rays and likely high-intensity solar particles events. The effects of this harsher radiative environment are amplified by other stress factors, such as altered gravity and transition between different gravity conditions, increased distance from Earth, prolonged spatial confinement and isolation. Together they may potentially trigger strong maladaptive biological processes, or even disease conditions[4,5]. Moreover, these critical environmental factors are detrimental to on-board equipment, including medical instrumentation and drugs, increasing the risk of health issues. In planning upcoming Lunar and Mars planetary missions, the potential human risks of exposure to dust, together with the impact on the functioning of equipment, should also be taken into consideration[6].

In this context, it is fundamental to understand the exact nature of the physiological changes induced by the space environment and the underlining mechanisms. To this aim, the development of innovative

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experimental models may contribute to deepening our knowledge of the molecular bases of the biological responses to the space exposome (the totality of human environmental exposures, complementing the genome[7]) and, enable testing of pharmacological and biomedical hypotheses in space as well as space analogues. The optimization of experimental platforms may help to overcome the ethical issues of animal and human research and exceed the constraints of logistics, resources and costs associated with space research. The identification of effective countermeasures is obviously a critical aspect to guarantee a safe and successful human presence in space.

Concerning pharmacological countermeasures, a deeper knowledge of the mechanisms of action of drugs and their pharmacokinetics in space will enable personalization of therapies, with optimized efficacy, tolerability and safety[8–11]. In addition to pharmacological countermeasures, also innovative technologies for physical therapies and nanotechnologies are promising solutions to counteract the negative effects of spaceflight.

Psychological well-being plays a crucial role, particularly during long-haul spaceflights. Psychological stressors, including isolation, confinement, disrupted circadian rhythms, and prolonged exposure to microgravity, can contribute to anxiety, depression, and cognitive decline. Furthermore, the interplay between psychological distress and physiological conditions may exacerbate health risks[12]. While psychological-related issues are not the focus of the present review, it is worth mentioning that current space missions involve psychological assessments, including mood and cognitive performance monitoring, future deep space missions require enhanced screening tools and intervention strategies to mitigate any potential risks. Ongoing research aims to refine real-time psychological evaluation methods, ensuring astronauts receive adequate support to maintain both mental and physical resilience throughout their missions[13].

Given the distance from the Earth and the delay in communications, future human space missions to the Moon and Mars require improved crew autonomy from ground support for mission management and for handling medical emergencies. New diagnostic and monitoring devices to treat medical issues are worthy of further development. Miniaturization, easy use, portability, wearability and in situ analyses capability are among the most important requirements for the development of multiparametric and integrated systems that can evaluate and preserve crew health and performance.

Advances in space medical devices and medications can also be translated to terrestrial applications[14], useful for example in the treatment of aging related diseases and in the management of medical issues in remote areas of the Earth or in situations where access to continuous medical assistance is limited. In this review we focus on the aforementioned issues, highlighting knowledge gaps that need to be filled to enable future long-term human space missions beyond LEO. In particular, the aetiology of space-related health issues need to be investigated, as well as drug stability, storage, production, efficacy and formulation for space application. Finally, the review provides recommendations for future research directions in the field of space life sciences, ranging from innovative in vitro and non-conventional in vivo models, to nanotechnology approaches, innovative therapeutic and diagnostic tools, tailoring also physical therapies devices to space environment.

Pharmaceutics

Astronauts can mitigate common disturbances induced by spaceflight, such as space motion sickness, sleep disturbances, allergies, pain, and sinus congestion, using the medications available on Earth. However, evidence suggests that drugs act differently in space and their efficacy may be decreased[8–11,14]. The effects of drugs commonly used on Earth could be different in space due to physiological changes induced by microgravity and other space environmental factors and stressors[14]. It is therefore important to investigate and understand why and how these differences occur, in order to optimise the dosage and/or the dose of a drug for a specific disease or condition. Inflight pharmacokinetics (PK) data have only been published for a few drugs[15]: scopolamine, used in combination with dextroamphetamine for the treatment of space motion sickness, and acetaminophen. The peak concentration (C_{max}) and time to peak concentration (T_{max}) were determined in saliva samples of astronauts after oral administration. For both drugs, a high variability of inflight versus on the ground PK were observed[12]. Interestingly, PK data may also vary depending on the duration of the space flight. Therefore, additional studies need to be conducted on the drugs that are part of the pharmacy for spaceflights. This may only be possible by acquiring information on the PK and pharmacodynamics (PD) of each active pharmaceutical ingredient (API) when used under conditions similar to those experienced on board[16]. However, ground-based studies, e.g., bedrest human studies, may reproduce only part of the environment and stressors of space flights and, whenever possible, a comparison with data generated in flight (e.g., on board the International Space Station - ISS) should be carried out to verify the validity of such studies[17].

Due to the limited number of studies on pharmaceuticals conducted in microgravity conditions, it is challenging to assess the effectiveness and stability of these medications during spaceflight[18]. The current lack of knowledge regarding altered PK/PD acts as a significant barrier to the successful treatment and prevention of medical events and robustness of any pharmacotherapy onboard[19].

Despite insights from various research in the field, significant gaps persist in our understanding of drugs PK/PD in space[18].

To address this unmet medical need, the introduction of protocols capable of evaluating the drug's PK– for instance, the dried urine spots (DUS) for the measurement of antihypertensive agents or the dried blood spot (DBS) methods[20,21] - in a microgravity setting have the potential to enhance personalized therapeutic approaches[18]. As a result, DBS and DUS represent a promising solution for conducting pharmacokinetic studies[20,21]. Their minimal biological sample requirements, lightweight, and extended stability make these two techniques particularly suitable for sample collection and storage onboard ISS[18] or future spacecrafts. Indeed, this approach allows clinical investigation to test and compare the same set of drugs administered in flight and on ground, providing valuable insights into whether there are any differences in drug efficacy between the two setting.

While the limited number of astronauts poses challenges for building robust predictive models, integrating knowledge about drug mechanisms, PK/PD profiles, and astronauts' genomic data could enable personalized medicine approaches. By leveraging pre-mission genomic and physiological assessments, in combination with Artificial Intelligence (AI) driven extrapolations from terrestrial databases, it is possible to tailor treatments to optimize efficacy, tolerability, and safety. Additionally, in-mission monitoring and adaptive modeling could further refine individualized therapeutic strategies over time.

Regarding logistics, a prolonged sojourn in space without the possibility of resupply from Earth poses a problem of ensuring availability of all potentially required medicines[22]. Moreover, the issue of stability of the Active Pharmaceutical Ingredient (API) over time, under conditions of microgravity and radiation exposure should be considered, both for standalone APIs and formulations. Stability data are already available for some drugs after prolonged storage on board the International Space Station (ISS), indicating that LEO spaceflight appears to accelerate the degradation of some medicines. Therefore, the risk of drug failure due to a reduction in API content must be considered. It must be noted that drugs tested for spaceflight stability are often removed from the manufacturer's packaging and repackaged into light weight containers[23]. Repackaging might influence the accelerated degradation of some APIs, and specific studies should be conducted to investigate this aspect. A recent paper examined the terrestrial shelf-life of the medications onboard the ISS[24]. As of 2023, more than half of the 111 medications listed in the formulary, expire within 36 months if stored in the manufacturer's packaging. This data indicates that studies on the possible ways to extend the half-life of APIs in space requires investigation for long-duration space flights. For any specific disease or condition, once the appropriate therapy has been identified, aspects such as mode of administration, monitoring of the effects of the therapy, and more generally monitoring the astronaut's health need to be addressed as they are critical for long-duration space flights.

Technologies for diagnostics

Diagnostic health technologies during space missions pose many challenges such as that of astronaut exposure to unique physiological and psychological conditions[4,25–28] and, limited availability of medical personnel, tools and equipment. The physical and psychological well-being of astronauts should be continuously monitored by advanced biomedical sensors and devices for an early detection of potential health issues and subsequent treatment to prevent escalation.In space missions, medical diagnostics tools can be classified as i) point-of-care (PoC) systems for assessing biological fluids ii) portable devices for imaging internal organs and their functions and iii) wearable sensors and skin electronics[29] (Fig. 1).

PoC systems are compact systems which provide rapid test results and real-time chemical, molecular and cellular analysis of body fluids for identification of pathogens, antigens/antibodies, infections and assessment of physiological functions[30]. Measurements of biomarkers such as specific enzymes, hormones, and proteins released in the body fluids after severe stress can be indicative, as an example, of heart damage or injury, vein thrombosis (DVT) or pulmonary embolism (PE)[31].

PoC systems exhibit limited sensitivity, specificity, and accuracy compared to standard laboratory-based equipment. However, a new generation of PoCs is being developed to perform accurate diagnostics and sensitive genetic analyses, crucial for monitoring astronaut's health and the spacecraft environment safety[32].

Several recent studies have identified in-flight genetic diagnostic methods. In particular, polymerase chain reaction (PCR), nanopore sequencing and CRISPR-based detection were shown to work successfully onboard the ISS[32–34]. Bacterial profiling using 16S sequencing and swab-to-sequencer experiments have also been accomplished[27,35]. Some recent genotyping studies based on nanopore sequencing, however, have reported discrepant results when compared to gold-standard short-read sequencing, highlighting the necessity of further development of the technology and validation concept when single-nucleotide resolution is critical[36].

Portable diagnostic imaging tools, such as ultrasound, help assess the physiological changes induced by the space exposome and detect potential injuries or abnormalities. Ultrasound (U/S) real-time non-invasive imaging of organs and muscles, has allowed real-time diagnosis in case of injuries or respiration problems[37] and cervical and lumbar spine imaging for back pain[38]. U/S-based methods have been exploited in space for measuring the jugular vein dimension[39] and for jugular venous blood flow stasis and thrombosis[40]. X-Ray imaging systems are an important alternative to U/S and, as they are now small and accurate enough to produce high quality images, they can be considered for implementation in spacecrafts and space stations[41].

Wearable sensors and skin electronics have emerged as promising tools for unobtrusively monitoring the health and well-being of astronauts during space missions. They offer real-time data collection and continuous monitoring, providing valuable insights into various physiological parameters. Wearable sensors, such as smartwatches, fitness bands, and chest straps, can track vital signs, physical activity, and sleep patterns. They allow astronauts and ground control teams to assess overall health, detect anomalies, and adjust interventions if needed. Furthermore, advances in skin electronics have led to the development of flexible, biocompatible devices that adhere directly to the skin. These skin-worn electronics can measure a wide range of physiological markers, including body temperature, muscle vibrations, arterial deformations, sounds produced by organs, hydration levels, and biomarkers present in sweat[42]. The integration of wearable sensors and skin electronics in astronaut health monitoring systems offers several benefits. Firstly, they enable continuous, non-invasive data collection, reducing the need for intrusive medical procedures. Secondly, they enhance the ability to detect health issues early, facilitating timely interventions to mitigate potential risks. Lastly, these devices aid in improving astronauts' performance and well-being by providing personalized feedback and optimizing their activity levels and sleep patterns[42,43]. Further technological developments are needed for wearable sensors and skin electronics to collect more reliable and accurate signals from the body in order to correlate them to pathophysiological conditions[44]. Data collected by equipment and sensors in space missions produces a real time instantaneous picture of the health condition. It provides early prompts of critical health issues and can be sent to control station and clinical experts to perform a more accurate analysis, diagnostics and prognostics. AI is playing a crucial role in space missions by analyzing vast amounts of health data collected from astronauts by edge computing. AI algorithms can identify patterns and trends indicative of potential health problems, providing early warnings to mission control. Importantly, AI systems can assist astronauts in making medical decisions based on their health data, enabling them to manage minor health issues independently and in real-time[44].

Technologies for therapies

There are therapies available on Earth that can be used as an alternative to drugs or in combination with them, to enhance their effects. Physical therapies including assisted exercise, ultrasound, magneto- and electro-therapy, and laser-therapy are applied worldwide to treat many acute and chronic diseases[45], decreasing pain, inflammation and oedema[46–49]. Compared to medications, physical therapies have fewer side effects and can be applied as the sole therapy or combined with other pharmacological and non-pharmacological treatments. While physical exercise is intensively used to counteract muscle atrophy and bone loss induced by space flight[50–53], other tools, such as laser therapy, magneto- and electro-therapy have not been considered for application in space due to technical and safety concerns. However, technologically advanced instruments of compact size are currently available on the market and are already used in public and private medical centres. Furthermore, personalized protocols can be implemented through the careful selection of treatment parameters. In space, physical therapies could be useful to reduce the use of drugs, help control pain symptoms and inflammation, speed up healing and also as a preventative measure for musculoskeletal problems[54]. To implement physical therapies in space further research efforts are needed to tailor the instruments to the environment of space vehicles and to test their effectiveness in space, although it can be hypothesized that there are fewer differences compared to drugs because the interaction between physical factors (laser radiation, electromagnetic fields) and biological tissues is direct and is not affected by processes of metabolization, accumulation, and excretion.

Physical approaches can often be coupled with nanotechnology, in particular, for the exploitation of "smart" nanoparticles and/or nanostructured materials[55].

On Earth, nanotechnology promises improved medical treatments and to date has provided many original tools (devices with at least one physical feature at the nanoscale, such as nanoparticles) and protocols for safe drug delivery, distribution, and clearance. It has also shown capability for acting on biological targets that are cells, organelles or molecules, recently achieving unprecedented spatiotemporal control of both nanotechnology devices and biological target functions[56]. Aiming at introducing a new generation of devices able to actively carry bioinstructive cues to their targets (and thus no longer working as passive carriers for medications), nanotechnology has driven the extraordinary development of multifunctional biomedical tools with inherent capabilities for both diagnosis and therapy, the so-called "theranostic" devices[57]. In space, nanotechnology could thus effectively meet the compelling needs of preservation and recovery of bodily structural and functional integrity in astronauts undergoing both short and long-duration spaceflight, by accomplishing multiple crucial duties in a harsh environment where support from Earth can be scarce or null.

In addition to the traditional requirements of medical devices, clarification of nanotechnology preparation stability in conditions of gravitational transitions (for instance, normal to hypergravity, and to microgravity) and of permanence in microgravity is mandatory for the application of these devices in real spaceflight scenarios. Nanoparticles enhance drug stability by protecting therapeutic/diagnostic agents from degradation, enzymatic processing, and environmental factors such as unfavorable pH and osmolarity values. Encapsulation within nanoparticles protects drugs from premature metabolization, extending their half-life and improving

Fig. 1 | Medical diagnostics tools for beyond-LEO space applications. Medical diagnostics tools that would be useful in space missions include point-of-care systems, portable devices for imaging and wearable sensors and skin electronics.

bioavailability[58]. In the near future, nanotechnology based novel device must prove resistance to radiation-induced damage, which can be also exacerbated in water-rich environments. Most importantly, the capability to retain theranostic properties and medicinal efficacy over long periods, such as those associated with interplanetary travels, must be demonstrated. Moreover, a critical issue to be addressed is related to the effects of altered gravity and radiation on the stability of nanoparticle dispersions, and most importantly on their interactions with cells and tissues. A recent study, for example, highlighted a substantial reduction in nanoparticle uptake by muscle cells following simulation of microgravity through a random positioning machine; these results highlight the need for a careful planning of dose and administration of nanomaterials-based treatments in space[59].

Among the desirable functions for nanotechnology medications amenable to spaceflight application, oxidative stress prevention and mitigation remain. Recently, the pivotal role of oxidative stress as a cause of several pathological conditions (alteration of the central nervous system homeostasis, and sarcopenia.) that affect astronauts[60,61] has been demonstrated. Increasing evidence supports the role of nanotechnology preparations in alleviating oxidative stress induced by spaceflight[62,63].

Technologies for trauma and medical emergencies

On exploration missions, medical evacuation to Earth will be unfeasible, and communication delay will make remote medical support less efficient. In this scenario, the crew will have to autonomously manage any health problems and emergencies.

Space agencies have conducted numerous studies to develop techniques, procedures and equipment to manage trauma and surgical emergencies aboard spacecraft/space bases, considering issues such as proper containment of the patient, caregivers, instruments and materials in microgravity, maintenance of sterility and waste disposal. The feasibility of several life-saving procedures has been assessed, and some of them, such as defibrillation, intubation, surgical suturing, or intravenous fluid administration are doable, albeit more slowly and with greater procedural complexity[64,65]. Methodologies have thus been developed to guide crewmen remotely. These training programs can provide the crew with diagnostic and operational aids but remain applicable only where real-time or near real-time communication is possible. Therefore, the development of new procedures, technologies, and equipment is mandatory in view of future space exploration missions beyond LEO. In particular, there is a need for multifunctional lab equipment, diagnostic imaging, analytical and emergency procedures matching the requirements for use on spacecraft in terms of security, miniaturization, ease of use/assisted use[66–69].

An additional crucial aspect will be the presence of medical personnel, or personnel with specific medical training, within the crew. This crew member should have the skills to make a diagnosis and decide on first aid interventions, countermeasures and appropriate therapies while waiting for a consultation with surgeons on Earth. For this purpose, knowledge of emergency medicine, internal medicine and aerospace medicine is required, as well as specific training in the use of all diagnostic and therapeutic tools present on board the space platform. Considering that, during future exploration missions, isolation and confinement will strongly affect the crew members psychophysiology and performance, the ability to recognize and alleviate psychological and psychiatric problems in other crew members will also be needed.

3D bioprinting for biomedical applications in space

3D printing in Space is considered an enabling technology for future missions to the Moon and Mars. For over a decade, studies in this area have been focused on the development of infrastructures[70]. More recent advances have enabled 3D bioprinting (that is 3D printing using biocompatible inks, which can contain one or more cell populations) to form 3D functional tissue constructs. Heart, muscle, kidney, skin, cartilage and other tissue analogs have been successfully printed on Earth. A crucial requirement for manned missions to Moon and Mars is the improvement of equipment and procedures for medical treatments on-board the spacecrafts or within future human settlements in extraterrestrial environments, since a rapid medical evacuation to Earth is not an option in case of severe injuries or illnesses. In this regard, 3D bioprinting is expected to have a significant role and space agencies have started to consider possible applications of 3D bioprinting technologies in space for the production of tissue constructs in a semi-automated manner[71]. Indeed, the possibility of creating tissue analogs that can be implanted to replace damaged tissues or to promote their regeneration is an attractive, yet challenging prospect. In this scenario, it would be fundamental also the development of instrumentation and surgical procedures to implant the grafts[69], techniques for in situ 3D bioprinting, as well as techniques for the maturation and long-term culture of tissue analogs. Nevertheless, 3D bioprinting in microgravity or partial gravity has the advantage of eliminating or minimizing the risk that the 3D bioprinted construct will collapse[72]. This is a particularly relevant advantage in the 3D printing of hollow structures, such as blood vessels and renal tubules, which are more difficult to bioprint than compact structures due to the risk of collapse. Despite the challenges that need to be overcome for clinical application, steady progress is being made in the field of 3D bioprinting in Space. For example a NASA 3D bioprinter is already in use on the ISS for biological 3D bioprinting experiments[73] and the European Space Agency is developing a facility for the long-term culture and maturation of tissue constructs in space[74].

In addition to the use of bioprinted tissue constructs for the treatment of injuries in astronauts, 3D bioprinting might be relevant for the production of 3D tissue models for basic research, e.g. for studying the effects of microgravity and cosmic radiation on cells and tissues and for pre-clinical investigation of drug effects in space[75].

Further experimental evidence is needed before bioprinting of tissues and organs may be considered as a safe technology for missions to the Moon and Mars. This will undoubtedly require extensive testing first in animal models both on Earth and in Space. After this stage and once the method is deemed safe in animal model, the use of bioprinted tissues/organs can be tested on Earth in humans.

New experimental models

Research conducted in space inevitably requires optimized biological platforms to test research hypotheses. Microfluidic devices, commonly referred to as Lab-on-Chip (LoC) systems, offer numerous advantages in microgravity when compared to traditional laboratory setups, such as a requirement for smaller sample and reagent quantities[76]. LoC integrates various laboratory processes and functions into a single chip, and this concept extends to applications in the biological domain, particularly integrating biological models into LoC systems.

In vitro models are widely considered to be a preliminary step in the path that leads to clinical tests. In addition to standard two-dimensional cultures, a number of comparatively more complex solutions have made their appearance in the recent scientific literature. The current trend is to replicate at least part of the complexity that is normally found in a real tissue[77]. For instance, by guiding cell growth through biocompatible and

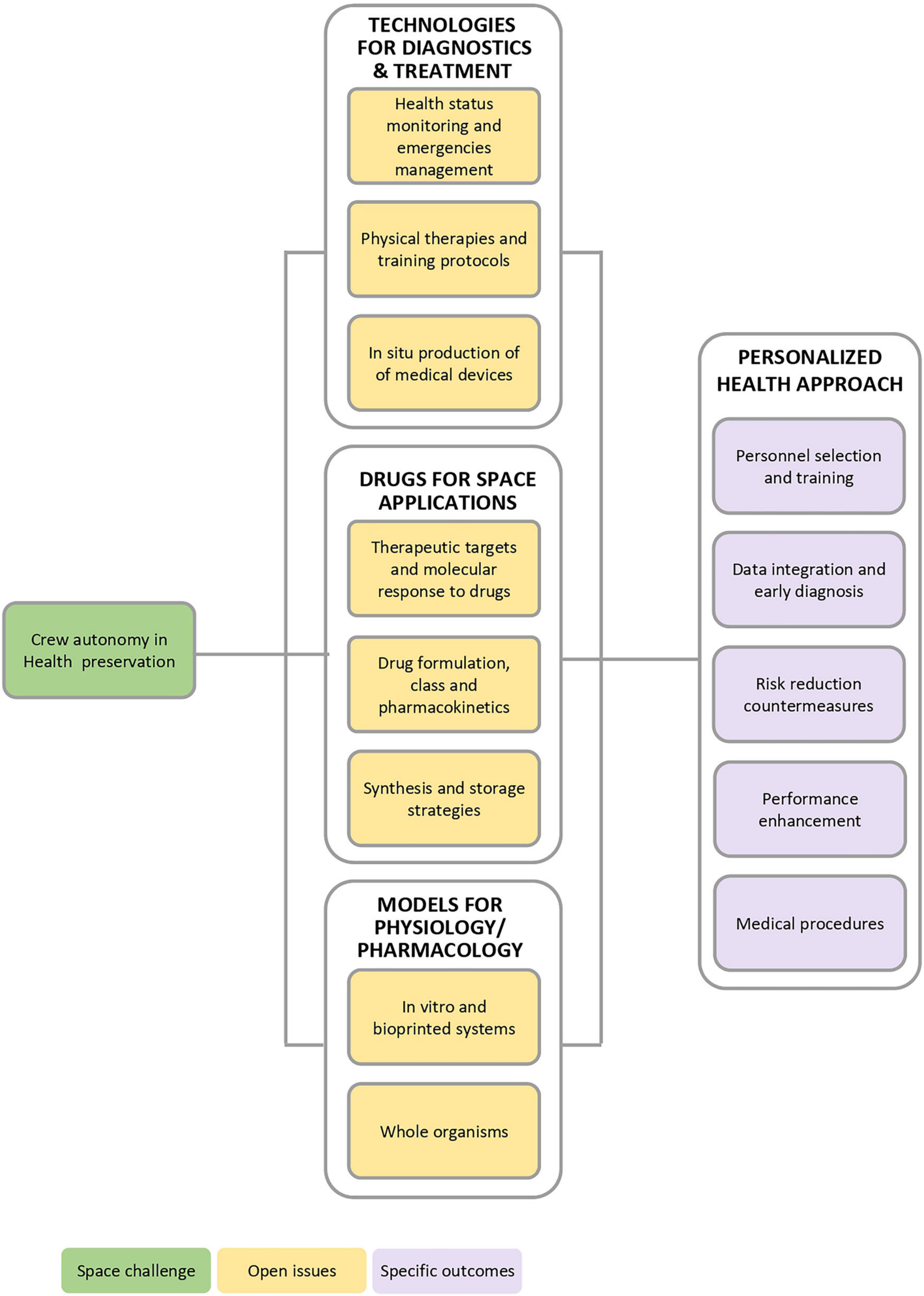

Fig. 2 | Main challenges for crew health in beyond-LEO missions. Graphical representation of the main challenges for crew autonomy in health preservation in space exploration missions beyond Low Earth Orbit.

three-dimensional scaffolds based on advanced molecular knowledge on cell commitment and differentiation, it is now possible to grow organ-like structures, generally referred to as organoids. Furthermore, the enhanced crosstalk between cell biology and engineering has extended the capabilities of the experimental models with the advent of the so-named organs-on-chips (OOCs)[78], which represent cutting-edge cell culture systems with significant potential. These can be based on biomimetic geometry, fluidics, co-presence of multiple cell types, smart materials, electronics, and artificial semi-permeable membranes.

OOCs, provide an ideal microenvironment to study the molecular and cellular activities underlying human organ functions[79]. Depending on the setup configuration, cells and macromolecules can be analyzed in situ, also by delivering known molecular signals and monitoring the induced effects in a controlled microenvironment[80]. This experimental approach also enables the replication of human-specific disease states, the identification of new therapeutic targets in vitro, and the prediction of human pharmacokinetic and pharmacodynamic responses to drugs.

In the near future, these capabilities may position OOC systems as an interesting alternative to traditional animal testing, especially in the context of long-term space missions. By harnessing the power of OOCs technology in combination with 3D bioprinting, we can potentially revolutionize medical capabilities and support self-sufficiency during human space missions beyond LEO, which is essential for the success of these missions[81].

These innovative technologies have been widely used to study the effect of microgravity on various models of human body tissues/organs/structures, providing invaluable insights for both space exploration and terrestrial studies[82–84]. One area of particular interest is muscle wasting in space, which has garnered significant attention. Researchers have employed electrical stimuli through electrodes to study in an OOC how to counteract muscle atrophy in microgravity, gaining valuable knowledge in this field[85]. Moreover, tissue-on-chips have become a model that can investigate the response of the immune system to microgravity, shedding light on its behavior and the potential implications for astronauts[86].

In parallel, scientists have directed their efforts towards modeling cardiomyopathies using human-induced pluripotent stem cells (hiPSCs) and investigating their response to microgravity conditions. This line of research has yielded crucial findings regarding the impact of microgravity on cardiac health[87]. Various experiments demonstrated that simulated microgravity induces significant alterations in hiPSC-derived cardiomyocyte functionality, including reduced contractile force and also induction of arrhythmias[88]. These findings suggest that microgravity serves as a unique environmental stressor that can accelerate the onset of cardiac pathologies, providing valuable insights for space medicine and terrestrial cardiovascular research.

Overall, the utilization of advanced technologies, such as OOCs and 3D bioprinting, to explore space environment effects on various human body organs/tissues/structures, has the potential to significantly advance our understanding of the effects of space travel on the human body. These advances will not only benefit space missions but also have implications for improving healthcare on Earth. By leveraging the insights gained from these studies, we can enhance medical interventions and develop novel treatments for conditions that affect both astronauts and people on Earth[81].

However, animal research remains essential given that the current in vitro systems, although sophisticated, do not allow for replication of a multi-organ system response to treatment as well as for behavioral studies. In this context, the use of invertebrates allows ethical issues to be overcome and reduces costs and logistic constraints for animal maintenance. They provide valuable and reliable models for genetic, aging, stemness, toxicology, cell biology, and drug discovery studies[89–92]. These considerations, valid for ground research, gain even more relevance in space, where logistic constraints are particularly restrictive.

Conclusions

Several biomedical challenges should be urgently addressed to enable long-term space missions (Fig. 2).

Little is known about the symptoms and signs of space-related medical conditions (e.g., muscle atrophy, bone loss, cardiac deconditioning), the precise aetiology and relative therapies. Gaps also exist in the knowledge of possible drug-drug interactions.

New in vitro cellular models, lab-on-chips, and organ-on-chips, in particular if coupled to computational approaches (i.e artificial intelligence), could be highly beneficial to investigate the health issues raising from human permanence in space environment. Non-conventional in vivo models, for example those based on invertebrates, can contribute to obtain reliable and reproducible results, with an approach that is, at the same time, void of ethical issues and simple in terms of the experimental setup.

Several questions concerning pharmaceutical aspects in space are still open: what is the impact of space on the stability of active pharmaceutical ingredients and excipients brought as stock? How to optimize storage and use of chemicals during long space missions? Are there drug classes or approaches that are more suitable for space? Can we formulate drugs in space (e.g., by mixing individual components or even by synthesis in situ)? All these issues are leading the use of "physical therapies" to be considered (for example based on laser, ultrasounds, etc.) for the treatment of a variety of pathological conditions that can affect astronauts.

The recent and fast development of nanotechnology may afford, thanks to the exploitation of "smart" and multifunctional nanoparticles, innovative therapeutic and diagnostic tools for the monitoring and preservation of astronaut health in the next future.

Lastly, new medical technologies for remote, non-invasive, and wearable diagnostics, medical emergency management, and data integration should also be developed to guarantee crew autonomy from Earth in health preservation.

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

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